THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—44TH YEAR SYDNEY, SATURDAY, SEPTEMBER 7, 1957 No. 10

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STUDIES ON PATTERNS OF FLUID INTAKE, WATER BALANCE AND FLUORIDE RETENTION.[1]

By NEIL D. CROSBY AND PHYLLIS A. SHEPHERD.[1]

From the Department of Physiology, University of Western Australia.

PART II: SWEAT AS A MEDIUM FOR THE EXCRETION OF FLUORIDE.

THE fluoridation of water supplies creates two special problems when applied in regions of such climatic conditions that the populace experiences a regular variation, from a season which evokes little or no sweating, to prolonged periods of considerable loss of fluid in the sweat.

On the one hand, the sweat loss calls for a replacement of body fluids, so that ingestion of fluoridated water is expanded. On the other hand, although it is known that the sweat is a potential vehicle for excretion of fluoride, very little information is available in quantitative terms. The situation is partly due to the considerable difficulties in mounting experiments for the collection of total body sweat in its original concentration.

Part I of this paper has indicated the magnitude and complexity of the problem of ingested fluids. The present section, some aspects of which were determined by the former part, demonstrates that a significant amount of the fluoride intake can be lost in the sweat. The results indicate that, to a limited extent, sweating can be considered as playing a part in the direction of an autoregulation of fluoride balance when fluctuating climatic conditions considerably vary the intake of fluoridated water supplies.

Methods.

The work was designed to investigate losses of fluoride via the urine and sweat. It consisted of three repetitions of experimental procedures by each of two subjects. The two factors which were varied in the experiments were sweating and dosage with fluoride. The dose was administered orally as three milligrammes of fluoride ion in the form of sodium fluoride solution. Urine was collected during twenty-four hours under the following four sets of conditions, each set being repeated three times: (i) no dose: no exposure to heat; (ii) no dose: collection of heat-induced sweat; (iii) dose given: no exposure to heat; (iv) dose given: collection of heat-induced sweat.

The two subjects, a male (N.D.C.) and a female (P.A.S.), refrained from the ingestion of tea and fish foods, to minimize their intake of fluoride from foodstuffs, before

[1] Work done with the aid of a grant from the National Health and Medical Research Council.

and throughout the experiments, which were conducted during the cool months, between late April and October. Physical activity was kept at a minimum, particularly on the days on which the experiments were performed. By these measures the skin loss of water outside the hot room was presumably very low, so that the sweat secreted during the experimental period approximated the twenty-four hour volume. When the subject was not exposed to heat, it was assumed that the renal loss of fluoride was the total twenty-four hour excretion. It is to be noted in this connexion that when the exposure to heat was terminated, the subject, after being washed with cool distilled water, left the experimental room, lightly clad, and his temperature rapidly reached normal. Dampness of the skin could not be detected visually or by palpation outside the experimental period, and it seems reasonable to assume that sweat losses outside this period were minimal. Both subjects attempted to stabilize their fluid intakes as far as possible during the experimental period, and avoided the ingestion of alcohol which might have provoked a diuretic response.

The dose was taken early in the morning after urine had been passed. When a dose was taken, the twenty-four hour urine volume was collected in two portions, one at three hours after the taking of the dose, the other during the remaining twenty-one hour period. When no dose was given, the twenty-four hour volume was pooled, and an aliquot used for analysis.

Collection of Sweat.

On experimental days when sweat was collected, the subject was thoroughly washed with tap water, then rinsed several times with double-distilled water, and dried with towels which had been washed previously in double-distilled water and oven-dried.

The collection of sweat was made in a waterproof plastic bag, approximately eight feet long by two feet wide, the top of which could be closed over the subject and sealed from the outside air. The bag had a hole at the level of the nose and mouth, to which was applied an inflated anæsthetic mask, strapped over the outside of the bag so that the subject could be sealed inside and yet had direct respiratory exchange with the outside air. Thus all the sweat, except that from the nose and from a small area around the mouth, was collected. Clinical and thermo-electric thermometers were inserted through the anæsthetic mask, so that oral temperatures could be recorded after the subject had been enclosed in the bag. The lower end of the bag was fitted with an outlet tube for draining off the sweat, this outlet being closed off during the experimental period. Between experiments the plastic bag was thoroughly rinsed with double-distilled water and dried.

Skin and air temperatures in several places within the plastic bag were recorded with thermocouple leads, which were passed down through the top of the plastic sack when the subject was placed inside. During the exposure to heat, the subject remained seated, and a head rest was provided.

Sweating was induced by maintaining the air temperature at about 40° C. in the small room where the experiment was conducted. The air in the bag rapidly reached saturation with moisture, and sweat began to run freely off the body within ten minutes after the bag had been closed. Ideally the exposure to heat would have provided volumes of sweat comparable in magnitude with those which are secreted during hot summer days. However, it was found that this method of sweat collection placed a considerable degree of strain on the body, and the subject became extremely conscious of his raised body temperature and of the circulatory adjustments which resulted from this heat load. With subject P.A.S. the experimental period had to be curtailed because of the distressing symptoms accompanying the rise in body temperature. The duration of exposure was thus determined by the subject's state and by his temperature, the run being terminated if the oral temperature rose above 103° F. The majority of the exposures lasted from one and a half to two hours.

The environmental temperature, skin temperature, oral temperature and pulse rate were taken at regular intervals throughout the exposure period, this being a necessary precaution, as both temperature and pulse rate tended to rise very rapidly, particularly after the first hour of exposure.

When the exposure to heat was finished, as much sweat as possible was drained to the bottom of the bag, and then emptied via the outlet tube into a polythene vessel. The bag was then opened, and the subject and the interior surfaces of the bag were thoroughly rinsed down with distilled water. The washings from the body and bag were then similarly collected in a separate polythene vessel.

The urine samples, the sweat and the body washings were all stored in polythene bottles in a refrigerator. If the samples were not analysed immediately, a few drops of toluene were added as a preservative. All samples were analysed within ten days of collection.

The urine and sweat were analysed for fluoride in duplicate (25 millilitre aliquots being used) by the method described by Smith and Gardner (1955). Prior to the actual determinations, recoveries of fluoride were made from standard sodium fluoride solutions and from specimens of urine with added fluoride. Recoveries ranged from 97% to 113% with a mean of 108%.

The concentrations of sodium, potassium and chloride were determined in the collected sweat, the sodium and potassium estimations being made with an EEL flame photometer. The chloride estimations were made after the method of Schales and Schales (1941).

The sodium concentration was also measured in the body washings. As the sodium concentration of the undiluted sweat was known, the sweat content of the body washings was calculated from the dilution factor and the volume of washings, it being assumed that the result was a near enough approximation to calculate the total sweat volume.

The sweat rate was calculated on the basis of the time interval from when the subject was first enclosed in the bag to the end of the experimental period. As the subject was prepared in the hot room, it was assumed that sweating would commence almost as soon as the subject was sealed in the plastic bag. This seems reasonable, because the subject was aware of rivulets of sweat within ten minutes.

Results.

The results of the several trials are given in Tables I to III.

Table I shows the total excretion of fluoride for each subject under the various conditions of the trial. Total excretion is presented as the urinary excretion of fluoride under cool conditions, or the sum of the urinary fluoride and sweat fluoride when the experimental conditions included exposure to heat. The mean total excretion taken from the three repetitions is given.

Statistical analysis of Table I has established that the second order interaction—that is, the interaction of individuals by doses by sweating—is highly significant, so that the effects of one factor must be examined separately at each level of the other factors. The least difference between two means of three observations which is significant is given as a footnote to Table I.

Thus, when the responses of the two subjects under the four experimental conditions are compared, the following observations can be made: (i) With no dose and no sweating, the total excretion of fluoride by the male subject was significantly greater than that of the female subject. (ii) With the conditions of sweating and no dose, there was no significant difference between the two individuals. (iii) With a dose of fluoride and no sweating, there was no significant difference between the two individuals. (iv) When the experimental conditions involved both a dose of fluoride and sweating, the male subject excreted a total amount of fluoride which was greater than the amount excreted by the female; the difference between the excretion of the two individuals was highly significant.

The effects of the administered dose on the total excretion of each subject under conditions of sweating and non-sweating were as follows: (i) The male subject did not excrete significantly greater amounts of fluoride when he received a dose if he was not sweating. However, when he was made to sweat, the fluoride loss was significantly greater after a dose of fluoride than it was when no dose was administered. (ii) The female subject, on the other hand, did excrete significantly greater amounts of fluoride after a dose, under both sets of experimental conditions; but the difference in excretion rate was greater under the conditions in which there was no sweating.

TABLE I.
Total Fluoride Excreted.

Subject.	Dose of Fluoride. (Milligrammes.)	Sweat.	Total Output of Fluoride in Milligrammes.			Mean.[1]
N.D.C., male.	0	−	1·098	1·480	1·832	1·470
	0	+	0·887	0·808	1·275	0·990
	3	−	1·863	1·732	2·096	1·897
	3	+	2·928	3·834	3·094	3·285
P.A.S., female.	−	−	0·660	0·747	0·486	0·631
	−	+	1·343	0·675	0·918	0·979
	3	−	1·716	1·848	1·928	1·831
	3	+	1·964	1·500	1·264	1·576

[1] The least difference between two means which is significant is: 0·524 ($P<0·05$), 0·722 ($P<0·01$), 0·994 ($P<0·001$).

Finally, the effect of sweating on the excretion of fluoride with and without a dose of three milligrammes of fluoride (as sodium fluoride) was as follows: (i) The male subject's excretion of fluoride was raised by sweating only after the administered dose. The increase was highly significant. There was no significant differences between the urinary loss and the urinary loss *plus* sweat loss when he was not receiving supplementary fluoride. (ii) Sweating had no significant effect on the total excretion of fluoride by the female subject.

It can be seen from Table I that only with the male subject did the total excretion of fluoride within twenty-four hours rise above three milligrammes. In the female subject the daily excretion was always less than two milligrammes.

Table II shows the concentration of fluoride in the sweat and urine, both with and without a dose of sodium fluoride. The volumes of sweat and urine are given, and also the output of fluoride in the two fluids is tabulated. The figures are derived from only that half of the trials for each subject in which there was exposure to heat.

An analysis of variance performed on the data for the output of fluoride in this table gives us the following information: (i) For N.D.C., the male subject, the level of excretion of fluoride in the sweat was significantly increased by an orally administered dose of fluoride. (ii) For P.A.S., the female subject, the increase in fluoride output in the sweat following a dose of fluoride was not statistically significant. (iii) Under the condition of no oral dose, there was no significant difference between the levels of output of fluoride in the sweat in the two subjects. (iv) For N.D.C., the increase in urinary output of fluoride following a dose was highly significant, while for P.A.S. the rise in fluoride output was not quite significant. (v) The urinary outputs of fluoride under the "no dose" conditions did not differ significantly between the two individuals, while with a dose the urinary output of fluoride by the male subject was significantly higher than that of the female.

Table III shows the fluoride concentration, after a dose, in the urine collected three hours after the administration of the sodium fluoride, and in the urine collected during the remainder of the twenty-four hour period. The volumes of these two urine samples are given, and the urinary output of fluoride during these two periods and the total twenty-four hour urinary output are also recorded.

The salient features of the analysis of variance of the data in Table III were a significant interaction between individuals and the time of urine collection (*i.e.*, collection at three hours or between three and twenty-four hours after the dose), and a significant interaction between individuals and sweating.

Both the subjects showed a significantly higher output of fluoride in the twenty-one hour sample than in the three-hour urine sample, the increase being significantly greater for the male subject than for the female subject.

There was no significant difference in the urinary excretion of N.D.C. when he was sweating, and when he did not sweat, while the urinary excretion of fluoride by P.A.S. was significantly lower when sweating occurred.

Electrolyte Losses.

Table IV is presented to indicate the conditions which held in relation to the secretion of sweat. The results listed in Table IV not only give the rates at which fluid can be lost through the skin under climatic stresses, but also they indicate the magnitude of the losses of three important electrolytes at different rates of sweating. In this connexion, at the only comparable rates of sweating for the two subjects there are statistically significant differences in the losses of the electrolytes. These differences are in keeping with the known variations due to differences in sex (Ahlman *et alii*, 1950).

Discussion.

Fluoride Excretion.

As the experiments were not balance studies, it was hoped by means of the precautions applied to the dietary habits of the subjects to reach a fairly stable output of fluoride under conditions in which no supplementary dose of fluoride was administered. In Table I, which shows the total amount of fluoride excreted under the various experimental conditions, it is apparent that a considerable variation in the daily fluoride excretion occurs when no dose is given. This variability of fluoride excretion when no dose is given is doubtless related to the diets of the subjects, and complicates the analysis of the effect of dose and sweating on fluoride excretion. McClure (1945) found that the fluoride excretion was higher when protein-rich diets were taken than with other diets. In view of the surprisingly high output of fluoride by N.D.C., who was taking a diet which excluded fish and tea, it is interesting to note that this subject had a high daily intake of protein material.

The urine volumes, when there was no sweating, are fairly uniform for each subject, with one exception in the case of P.A.S. The urine volumes collected on days when there was sweating, although considerably lower, are likewise fairly uniform.

The duration of exposure to heat was determined by the subject's ability to tolerate the experimental conditions. The rise in body temperature was rapid, as the high environmental temperature and the 100% humidity did not allow any cooling of the body. The volumes of sweat collected from N.D.C. ranged from 990 to 1671 millilitres. This would be less than maximal twenty-four hour losses for this subject in hot weather, as calculated from the fluid intake and output studies, but is greater than his mean daily loss in summer. Subject P.A.S., on the other hand, provided much smaller volumes of sweat, between 240 and 611 millilitres, volumes which are very much less than the calculated summer sweat losses.

In studies on three adults and a group of adolescent girls (see Part I of this paper), the maximum intakes of water and of fluids which are mainly water were between 2·5 and 4·5 litres—a level of ingestion which would provide

TABLE II.

Fluoride Excretion in Sweat and Urine.

Subject.	Dose of Fluoride. (Milligrammes.)	Fluoride Concentration in Sweat. (Parts per Million.)	Volume of Sweat. (Millilitres.)	Output of Fluoride in Sweat. (Milligrammes.)	Fluoride Concentration in Urine. (Parts per Million.)	Twenty-four-Hour Urine Volume. (Millilitres.)	Twenty-four-Hour Output of Fluoride in Urine. (Milligrammes.)
N.D.C.	0	0·30	1110	0·333	0·64	865	0·554
	0	0·47	990	0·455	0·49	720	0·353
	0	0·72	1035	0·945	0·40	825	0·330
	3	0·93	1280	1·190	2·16	806	1·738
	3	1·14	1671	1·905	2·24	859	1·929
	3	0·98	1494	1·464	1·63	1000	1·630
P.A.S.	0	0·91	240	0·218	1·47	765	1·125
	0	0·51	425	0·216	0·85	540	0·459
	0	0·84	611	0·513	0·90	450	0·405
	3	1·71	503	0·860	1·83	602	1·104
	3	1·24	434	0·538	1·43	674	0·962
	3	1·45	357	0·518	1·20	623	0·746

between 2·5 and 4·5 milligrammes of fluoride if the water was fluoridated at one part per million. These results led to the choice of three milligrammes of fluoride as a convenient dose.

In the present investigation, the daily excretion of fluoride, when no dose was administered, varied between 0·631 and 1·470 milligrammes. These values are higher than those given by Machle, Scott and Largent (1942), but are within the range of normal excretions given by Hodge (1956). This level of excretion appears to be rather high for these subjects, who were resident in an area where the water supply is almost fluoride-free, and who were abstaining from foods known to contain appreciable quantities of fluoride. The level of total excretion of fluoride when no dose was administered was not significantly affected by sweating in either subject, so that fluoride excretion under conditions of no dose was affected only by the fluoride content of the diet, and not by the experimental treatment.

After a dose of fluoride had been administered to subject N.D.C., there was a significant sweat effect in removing this fluoride from the body. N.D.C. secreted fairly large volumes of sweat in short periods of time, and by this means was able to excrete considerable quantities of fluoride. The concentration of fluoride in this sweat was between 0·93 and 1·14 parts per million, which is within the ranges of concentration quoted by both McClure (1945) and Machle and Largent (1943), but exceeds their mean values.

The twenty-four hour renal excretion of fluoride by N.D.C. was not significantly changed by sweating when a dose was given. When there was no sweating, the renal loss constituted the twenty-four hour excretion, and retention obviously occurred. When N.D.C. sweated, the fluoride lost in the sweat together with the fluoride excreted in the kidney was over three milligrammes. Thus, when N.D.C. was exposed to a high environmental temperature, the amount of fluoride retained decreased. The actual

TABLE III.

Urinary Excretion of Fluoride After a Three-milligramme Dose.

Subject	Sweating.	Fluoride Concentration in Urine I.[1] (Parts per Million.)	Volume of Urine I. (Millilitres.)	Output of Fluoride in Urine I. (Milligrammes.)	Fluoride Concentration in Urine II.[2] (Parts per Million.)	Volume of Urine II. (Millilitres.)	Output of Fluoride in Urine II. (Milligrammes.)	Twenty-four Hour Output of Fluoride. (Milligrammes.)
N.D.C.	0	1·19	235	0·280	1·46	1084	1·583	1·863
	0	1·15	255	0·293	1·37	1050	1·439	1·732
	0	1·12	390	0·437	1·36	1220	1·659	2·096
	+	1·31	226	0·297	2·49	580	1·441	1·738
	+	1·24	74	0·092	2·34	785	1·837	1·929
	+	1·60	240	0·384	1·64	760	1·246	1·630
P.A.S.	0	1·91	286	0·548	1·17	998	1·168	1·716
	0	2·49	237	0·590	1·92	658	1·258	1·848
	0	4·03	205	0·826	1·45	760	1·102	1·928
	+	2·40	102	0·244	1·72	500	0·860	1·104
	+	1·97	94	0·185	1·34	580	0·777	0·962
	+	1·06	93	0·099	1·22	530	0·647	0·746

[1] Urine I = urine volume collected three hours after ingestion of the dose.

[2] Urine II = urine passed in remaining twenty-one hours of twenty-four-hour period after the dose.

quantity of fluoride retained cannot be assessed, as the dietary fluoride intake could not be stabilized.

With subject P.A.S. the secretion of sweat did not significantly change the total output of fluoride after a dose of three milligrammes. Although over 0·5 milligramme of fluoride was lost in the sweat after a dose of three milligrammes, the total of sweat and urinary output of fluoride did not differ significantly from the urinary output of fluoride when the subject was not exposed to heat (Table I). Therefore, for this subject, when sweating occurred, the renal output of fluoride was diminished.

Excretion of Fluoride Under Conditions of Sweating.—After a dose of fluoride the sweat output of fluoride was increased for both subjects (Table II); but only in the case of N.D.C. was the increase statistically significant. Although the output of fluoride in the urine, without added dose, was similar for both subjects, N.D.C. exhibited a significant increase after the dose, but P.A.S. did not (Table II). The total excretion of fluoride by N.D.C. greatly exceeded that of P.A.S. The reasons for the differing responses are not apparent, although such factors as age, sex, size, rates of absorption, rates of sweat secretion, *etc.*, may be contributory. Although no skin loss of water was detected outside the periods of sweat collection, it is quite feasible to assume that the skin loss could be slightly higher than that measured during the experimental period. If any such loss of water and so of fluoride occurred, it would lower the apparent retention of fluoride, but it is doubtful that it would in any way minimize the differences observed between the two subjects studied.

Excretion of Fluoride Under Conditions of Dosage with Fluoride.—Analysis of data from Table III shows that the urinary excretion of fluoride by N.D.C. after dosage with fluoride is unaltered by sweating, but that in the case of P.A.S. the excretion is significantly lower when she sweats. This information indicates that P.A.S. tends to store fluoride more than does N.D.C.

Hodge (1956) reports that after ingestion of a dose of fluoride the urinary level is elevated within one hour, and one-quarter of the dose will be excreted via the kidneys within three hours, while the remainder of the dose is lost within twenty-four hours. In Table III are given the urinary output of fluoride in the first three hours after ingestion of the dose, and the fluoride output in the urine collected in the next twenty-one hours. The output of fluoride in the first three hours was less than 0·6 milligramme in 11 of the 12 observations—that is, less than one-fifth of the administered dose. The mean excretion of the three-hour period is about one-seventh of the presumed ingested dose. These findings indicate that for these subjects the urinary excretion of fluoride immediately after the dose is less than would be anticipated from the results of Hodge.

The data collected in this experimental work are not strictly comparable with the balance studies on humans which have been carried out up to date, because a true balance has not been studied, nor have repetitive daily doses of fluoride been given. Only the excretion within twenty-four hours after a single dose has been examined. Data from other workers (Machle and Largent, 1943) have indicated that upwards of 90% absorption can be expected from aqueous solutions of sodium fluoride. In all the discussion of retention, the near-total absorption of the dose has been assumed. However, the percentage absorption would obviously affect the level of retention which was observed. The lack of knowledge as to the exact amount of fluoride derived from dietary sources has been mentioned; this is another factor which complicates the evaluation of the retention which occurred with the two subjects used in this investigation.

Examination of the total output of fluoride after a dose of three milligrammes of fluoride, irrespective of sweating, indicates that both subjects retained substantial amounts of fluoride. Although N.D.C. excreted over three milligrammes in urine and sweat, if his dietary fluoride intake was to give fluoride excretion comparable with that observed in experiments with no dose, then some of the total ingested fluoride must have been retained. There is difficulty in establishing a minimum dose of fluoride which will result in retention. Largent and Heyroth (1949) did observe retention on a supplementary dose of three milligrammes of fluoride when sweat was not measured, a finding which the results here appear to confirm. On the other hand, Machle, Scott and Largent (1942) observed that it required some days for the urinary excretion to become stabilized; thus the retention observed in the present experiments could have occurred merely because a single dose was used. If the same subjects were given repetitive doses, would the level of excreted fluoride become stabilized so that no retention would occur after the preliminary stabilizing period?

TABLE IV.

Sweat, Sodium, Potassium and Chloride.

Subject.	Dose. (Milligrammes.)	Sweat Rate. (Millilitres per Hour.	Sodium. (Milliequivalents per Litre.)	Potassium. (Milliequivalents per Litre.)	Chloride. (Milliequivalents per Litre.)
N.D.C., male.	0	416	72·2	5·0	68·8
	0	495	71·7	5·4	60·9
	0	668	93·4	5·4	83·8
	3	668	92·4	6·0	81·8
	3	771	97·8	5·5	86·3
	3	700	95·6	5·4	85·7
P.A.S., female.	0	131	43·9	11·5	38·9
	0	268	54·3	9·6	49·8
	0	386	49·2	8·7	46·7
	3	377	46·6	8·9	53·5
	3	289	61·7	8·9	54·5
	3	214	54·1	9·5	49·0

Conclusion.

From these studies, it is evident that significant amounts of fluoride do appear in the sweat. Up to 50% of the total fluoride excreted appeared in the sweat, a value which is higher than reported by McClure *et alii* (1945). This high value for sweat loss may well result from the very high rates of sweating which were induced at a time when presumably the blood level of fluoride was at a maximum—namely, one hour after the ingestion of the dose. The results for N.D.C. also indicate that neglect of skin losses of fluoride may give a completely erroneous balance for fluoride in summer weather. The result for P.A.S. indicates that retention can occur on a daily dose of three milligrammes of fluoride, even when sweat losses are included—a finding supported by the studies of Largent and Heyroth (1949), but contradicted by McClure *et alii* (1945).

In general, the subject N.D.C. (a male, aged forty-three years) showed less tendency to apparent storage of fluorine, especially under conditions of sweating, than did subject P.A.S. (a female, aged twenty-two years). It may be that the older subject has higher bone concentration of fluoride and hence less tendency to "trap" fluoride after a dose. In neither case is there any knowledge of total previous exposure to fluorine, although for several antecedent years both subjects have been resident in an area where the public water supply is almost free from fluoride.

Summary.

1. The excretion of fluoride is reported for a male and a female subject under planned conditions, with and without sweating, and with and without an oral dose of three milligrammes of fluoride ion.

2. Figures for whole body sweat and for urine are given; a method for the collection of whole body sweat is described.

3. Significant amounts of fluoride were excreted in the sweat; up to 50% of the administered dose was recovered in the sweat of the male, whose mean output exceeded previously published figures.

4. There were significant differences between the two subjects, possibly due to sex differences.

5. The losses in sweat revealed in the work suggest that sweating plays a real part in the direction of auto-regulation of fluorine balance when climatic conditions seriously vary the seasonal intake of fluoridated water supplies.

Acknowledgements.

We should like to thank the following: Mr. N. S. Stenhouse, of the Commonwealth Scientific and Industrial Research Organization, for statistical analysis of the results; Mrs. J. Barker and Mr. J. Marsh, of the Physiology Department, University of Western Australia, for assistance during experimental periods; Miss A. Little, of the Psychology Department of the University of Western Australia, for cooperation in the collection of data from a group of pre-school kindergarten children; the Methodist Ladies' College, Claremont, Western Australia, for cooperation in the collection of data from a group of schoolgirls. In addition to the major support from the National Health and Medical Research Council of Australia, we wish to acknowledge assistance from a research grant from the University of Western Australia.

References.

AHLMAN, K. L., EVÄNKÖ, O., KARVONEN, M. J., and LEPPÄNEN, V. (1953), "The Mineral Composition of Thermal Sweat", *J. Clin. Endocrinol.*, 13: 773.

HODGE, H. C. (1956), "The Metabolism of Inorganic Fluorides", *J. Am. Dent. A.*, March: 307.

LARGENT, E. J., and HEYROTH, F. F. (1949), "The Absorption and Excretion of Fluorides III. Further Observation on Metabolism of Fluorides at High Levels of Intake", *J. Indust. Hyg. & Toxicol.*, 31: 134.

MACHLE, W., SCOTT, E. W., and LARGENT, E. J. (1942), "The Absorption and Excretion of Fluorides I. The Normal Fluoride Balance", *J. Indust. Hyg. & Toxicol.*, 24: 199.

MCCLURE, F. J., MITCHELL, H. H., HAMILTON, T. S., and KINSER, C. A. (1945), "Balances of Fluorine Ingested from Various Sources in Food and Water by Five Young Men; Excretion of Fluorine Through the Skin", *J. Indust. Hyg. & Toxicol.*, 27: 159.

SCHALES, O., and SCHALES, S. S. (1941), "A Simple Accurate Method for the Determination of Chloride in Biological Fluids", *J. Biol. Chem.*, 140: 879.

SMITH, F. A., and GARDNER, D. E. (1955), "The Determination of Fluoride in Urine", *Am. Indust. Hyg. A. Quart.*, 16: 3.

TROPICAL ULCER AMONGST THE NATIVES OF NEW GUINEA.[1]

By JEKABS KARIKS,

Department of Public Health, Territory of New Guinea.

IN its prevalence and the prolonged incapacitation to which it gives rise, tropical ulcer must be regarded as a social disease of the first rank amongst the native population of New Guinea. Between one-third and one-half of all patients in the hospitals at any given time are suffering from tropical ulcer.

Tropical ulcer of all diseases is the most neglected by all parties involved—the native patient himself, the employer and also the hospital staff. As tropical ulcer is so prevalent, the natives themselves do not regard it as a disease for which they should seek medical help, so long as it does not cause too much pain, to which they are fairly indifferent. They accept it more or less as bad luck which has befallen them or their family. The employer thinks that a sore on the leg is not a serious enough condition to send a man to hospital for some weeks; and the hospital staff thinks frequently that a tropical ulcer is not a serious enough disease to warrant much attention to its treatment.

In this paper an attempt is made to describe tropical ulcer as it is seen amongst the native population of New Guinea, to discuss the causes and treatment, and to review briefly the literature of the last ten years.

Definition.

Tropical ulcer is an acute, specific, inflammatory, ulcerative process, involving the skin and the subcutaneous tissues, with characteristic adherent, foul-smelling slough overlying a soft, very tender and easily bleeding granulomatous base with surrounding œdema, caused by spirochætes and fusiform bacilli. If it is neglected, this process spreads quickly to involve also the underlying tendons and muscles, and if it is further neglected, even bones. If the process is only partly arrested, the ulcer becomes secondarily infected, and it may develop into a chronic, non-specific ulcer indistinguishable from indolent ulcers resulting from other causes.

Geographical Distribution.

Tropical ulcer is met throughout the Territory of New Guinea.

Ætiology.

Amongst other organisms, diphtheroid bacilli and *Corynebacterium diphtheriæ* have been named as the causative factors. Magara *et alii* and Wu *et alii* thought that a specific organism, *Diplococcus tropicus*, was the causative organism. Many workers have found in the smears streptococci and staphylococci together with other organisms. The writers who have made serious attempts to identify the causative organisms have agreed that they are spirochætes and fusiform bacilli and that there are some other predisposing causes. In every one of 50 cases which were investigated for microorganisms, spirochætes and fusiform bacilli were seen (Table I).

The still existing disagreement about the causative factor lies in the fact that most of the writers dealing with this question have omitted to state whether their findings were made in acute or in chronic ulcers. In chronic, secondarily infected ulcers, one rarely, if at all, will find spirochætes and fusiform bacilli, but all kinds of other organisms—for example, diphtheroids, streptococci, staphylococci, *etc.*, will be found. One must also be careful in taking the smears for microscopic examinations. The smears taken from the surface of the slough will always contain other microorganisms besides the spirochætes and fusiform bacilli, if the last-mentioned are to be seen at all. As the spirochætes and fusiform bacilli are anaerobic organisms, they are to be looked for in the deep layers of the slough and in the inflamed tissues.

It has also been proved experimentally (Vincent, Lichtman, Panja, Mohanty) that it is possible to cause a tropical ulcer in a healthy man if spirochætes and fusiform bacilli are inoculated in the skin or smeared on the previously scratched or crushed tissues.

Predisposing Causes.

Besides the causative microorganisms, the predisposing causes are of the highest importance in the incidence of tropical ulcer. They may be summed up in the following order of importance:

1. Trauma. About 94% of all patients with an acute tropical ulcer, on being questioned, admitted that they had received some injury prior to the onset of the acute inflammation. Only a small fraction (12 out of 150 patients questioned — Table II) could not remember having received any injury; but they also could not deny it. Some kind of skin lesion—*e.g.*, an insect bite with scratching afterwards—is enough to permit the infectious organisms to set up inflammation. Trauma is essential for the infective organisms, as it helps to create the ground for their anaerobic existence. The local blood circulation is dis-

[1] An extensive bibliography compiled by the author has been omitted to conserve space.

turbed for long enough to avoid the destruction of the infective organisms. As all the native population walks barefooted, there is plenty of opportunity to sustain a small injury to the foot or to the lower part of the leg.

2. Hygiene. It is no secret that the sufferers from tropical ulcer are also the dirtiest people of the village or on the plantation. Tropical ulcer is rarely or never seen amongst people who observe the minimum hygiene requirements in the tropics. People who wash themselves at least once a day and who take care to apply a clean dressing with some antiseptic on injuries sustained, are not amongst the ulcer patients.

TABLE I.

Organisms Found.	Number of Cases.
Spirochætes and fusiform bacilli	43
Fusiform bacilli alone	7
Total	50

3. Climate. It is surprising to observe the steep increase in the rainy season in new admissions to the ulcer wards for acute tropical ulcer. Tropical ulcer is more prevalent in the hot and humid areas. Although tropical ulcer is seen also amongst the inhabitants of highlands and in more moderate climates, it is rarely seen outside latitudes 35° north and 10° south (Lichtman). The disease disappears under conditions of extreme heat, cold or dry climate. That the hot and humid climate plays an important part in the incidence of tropical ulcer is easily understood from the fact that the skin is permanently macerated and irritated by perspiration, itching is increased and the causative organisms have much more chance of remaining viable.

TABLE II.

Type of Trauma.	Number of Cases.
Cuts	73
Scratches	38
Contusions	27
Subject could not remember	12
Total	150

4. Blood circulation. As has already been mentioned, impaired blood circulation promotes the growth of infective organisms. Golden *et alii* and Lipping and Ransford regard this condition as of primary importance. It has been observed that the lower part of the front of the leg and ankles is supplied by the terminal blood vessels of the adjoining arteries, which do not overlap and are unusually well supplied with vasoconstrictor fibres. In this area also the incidence of tropical ulcer is very high. It is, then, understandable that even the slightest trauma in this area may cause serious local circulatory failure.

5. Malnutrition and lack of vitamins. There is a very widespread belief amongst the workers who have written about the tropical ulcer that malnutrition and lack of vitamins play an important part as a predisposing cause. Most of their expressed opinions are more suggestions and beliefs than the results of investigations. Some investigations (Blank, Berry, Adamson) have produced no evidence supporting these opinions.

Amongst the native population of New Guinea there is no malnutrition, and cases of avitaminosis have very rarely been observed. Tropical ulcer is seen amongst people who are well fed and whose diet is rich in animal proteins, as well as amongst people whose diet is mainly vegetarian. No advantage in the healing of tropical ulcer was observed amongst patients to whom vitamin *B* and vitamin *C* were administered by mouth in addition to the usual treatment; the same observation applies to vitamin *E*.

The explanation of the fact that debilitated people more frequently suffer from tropical ulcer than do normal people may be that the exhausted body shows no resistance against the infective organisms, and that an exhausted person has lost much of his vital capacity and many of his interests, and has not the necessary will-power to avoid infection.

6. Hypoproteinæmia. There is also a very widespread belief amongst different writers that natives suffer from hypoproteinæmia; but there is not much evidence that this is so, as very little work has yet been done on serum protein content amongst the native populations. Those workers who have undertaken some investigations (Montestruck *et alii*, Linhard *et alii*, Arens *et alii*, Bernson *et alii*, Le Gac *et alii*, Lanzo, Charmot *et alii*, Brussou *et alii*) have found that the total serum protein contents were within normal limits or increased. They have also found that the serum protein ratio was abnormal, although no satisfactory explanation for this abnormality could be given. Usually the serum albumin level was slightly decreased or within normal limits, but the serum globulin contents were increased.

In the present study, 73 patients suffering from tropical ulcer were investigated (Table III). If total serum protein contents of 6·5 to 7·5 grammes per 100 millilitres are accepted as the normal limits, then only six of the 73 patients were found to have total serum protein contents within normal limits. One patient, who also suffered from chronic nephritis with gross albuminuria, had a total serum protein content of 5·9 grammes per 100 millilitres. Sixty-seven patients were found to have total serum protein contents above the accepted normal limits, mostly between 7·5 and 10 grammes per 100 millilitres. One patient had a total serum protein content of 12·6 grammes per 100 millilitres. The total serum protein estimation was carred out by the copper sulphate method as described by Phillips *et alii*.

The serum electrophoresis patterns from six patients indicated a substantial increase in β and γ globulins.

The idea that these proteins may be of low biological value, as suggested by Lichtman, needs further investigation. In none of the cases investigated, except the case of chronic nephritis, were any signs of protein deficiency or disturbed equilibrium (œdema *etc.*) seen.

Age and Sex.

The age of the patient plays a minor part in the incidence of tropical ulcer. All age groups are affected. Tropical ulcer is a comparatively rare disease amongst children aged under five years and in the aged. Young people aged between fifteen and forty-five years are mostly affected. Smaller children are usually carried around by their parents and have less chances of sustaining the necessary trauma. Amongst aged people also tropical ulcer is a rare disease, as they are more or less cut off from active pursuits. These people usually suffer from old and chronic ulcers and from disabilities caused by ulcers in their younger years.

In cities and on plantations sex has some influence. There the male, being more active, is also more frequently affected. Amongst village natives, where the female is as active in garden work as the male, the incidence of tropical ulcer is equally distributed between both sexes. Tropical ulcer affects rural more frequently than urban populations because of their different occupations, living standards and more easily accessible medical aid.

Location.

Most workers have agreed that tropical ulcer is a disease affecting only a particular part of the body—the dorsum of the foot, the toes, the ankles and the lower third of the leg. Some few workers have also observed tropical ulcer on other parts of the body. Other sites, although described, are most unusual, and closer examination would probably have revealed a mistaken diagnosis.

An important feature of tropical ulcer is that only one usually occurs at one time. In very rare cases multiple lesions, usually chronic, may be observed. They are then usually on the same limb and close one to another.

Tropical ulcer leaves no immunity.

Symptoms.

The most characteristic and unforgettable symptom of an acute tropical ulcer is the nauseous smell. It may be diagnosed from a distance when the patient is still out of sight. The pain is of importance, as it influences the sick person to seek medical help and relief. Pain may be of such intensity that even the most robust patient will seek a doctor's help after two or three days' hiding. Another important symptom is the characteristic blood-stained, greyish phagedenic slough, which liquefies on the surface and runs down the affected limb, attracting scores of flies. Usually there is also œdema around the ulcer. The margin and base of the ulcer are highly tender and granulomatous and bleed easily. Almost never is any lymphangitis or swelling of regional lymph glands associated with tropical ulcer. The general health of the patient is not impaired.

TABLE III.

Case Number.	Serum Protein Content. (Grammes per 100 Millilitres.)	Case Number.	Serum Protein Content. (Grammes per 100 Millilitres.)	Case Number.	Serum Protein Content. (Grammes per 100 Millilitres.)
1	7·8	26	7·4	50	8·5
2	9·7	27	9·3	51	8·9
3	10·4	28	10·0	52	8·9
4	10·0	29	7·8	53	8·5
5	9·6	30	8·9	54	8·2
6	9·6	31	7·2	55	8·2
7	8·9	32	8·0	56	5·9
8	9·6	33	8·9	57	7·2
9	10·4	34	8·2	58	6·8
10	8·9	35	7·4	59	8·0
11	10·2	36	7·8	60	8·5
12	9·8	37	8·2	61	7·8
13	8·5	38	7·8	62	8·2
14	8·5	39	8·5	63	11·0
15	8·2	40	7·8	64	9·3
16	8·9	41	8·2	65	10·5
17	8·5	42	8·9	66	10·6
18	7·8	43	7·8	67	12·6
19	7·8	44	8·5	68	9·3
20	8·7	45	7·8	69	8·9
21	8·9	46	9·3	70	7·8
22	8·2	47	8·5	71	8·9
23	9·3	48	8·2	72	10·0
24	8·9	49	6·2	73	8·9
25	8·5				

Diagnosis.

In an acute tropical ulcer the diagnosis is unmistakable: once seen, once smelled, never forgotten.

Differential Diagnosis.

In acute and early cases tropical ulcer may be mistaken for cellulitis. Furunculosis, too, may be diagnosed. When an acute tropical ulcer is located on a toe, a diagnosis of gangrene may be made. This is actually not wrong. When the ulcer is located over the proximal phalanx of a toe, an unnecessary amputation may be considered or even performed. If the ulcer is treated vigorously and early enough, amputation of the affected toe will very rarely be necessary.

The most common mistakes in diagnosis are made in cases of chronic ulcer. In New Guinea tertiary yaws lesions are mainly misdiagnosed as tropical ulcer. This error may be avoided by keeping in mind the fact that tropical ulcer is a single lesion and is located on the foot or on the lower part of the leg. Tropical ulcer is a typical ulcer with loss of tissues. Yaws lesions are almost always multiple and only rarely single. Yaws lesions are located on the lower parts of the legs as well as on other parts of the body—*e.g.*, thigh, calves, buttocks, forearms, *etc.* Yaws lesions are granulating, hypertrophic sores. The chronic, secondarily infected tropical ulcer usually has a scanty discharge. Yaws lesions, on the other hand, have a profuse, sweaty-smelling, thin, yellow discharge. Around the tropical ulcer of longer standing usually there are sclerotic scar tissues. Around the yaws lesions the skin is normal; seldom is there a sclerotic scar. Ulcers caused by yaws heal very slowly on tropical ulcer treatment, and heal smoothly if yaws treatment is initiated.

Cutaneous leishmaniasis may cause similar difficulties in areas where it is prevalent.

Veldt sore is confined to dry and desert areas where there is no tropical ulcer.

In all other sores on legs, except those caused by varicose veins (which are practically unknown in the Territory of New Guinea and most uncommon in the tropics), misdiagnosis has no adverse effect, as the treatment is more or less on the same lines.

Prognosis.

The prognosis is good if proper action is undertaken to arrest and control the infection. In cases in which the infection is permitted to spread unchecked, great damage may be caused to the affected limb. If it is unchecked, the infection spreads very rapidly, involving the underlying tendons and muscles and also the bones, and causing periostitis and later osteomyelitis with sequestration. The main danger lies in the disfigurement and incapacity to which these uncontrolled infections may lead (Figures IA and IB). Life becomes endangered when carcinoma develops on long-standing, neglected, chronic tropical ulcers. An amputation of the foot or of the lower part of the leg may be necessary, especially in children, when the sore has been neglected and the blood circulation of the distal parts disrupted. (I observed a recent case of this type. The patient was a girl, aged seven years, who was neglected in the village for two weeks; gangrene of the foot necessitated an amputation.)

Treatment.

Not in the standard text-books on tropical diseases, in the current medical literature, or in the past has there been any unanimity about the treatment of tropical ulcer. As many different treatments have been suggested as there have been writers on this subject.

Actually, the question to be answered is not how to cure the tropical ulcer, but in how long or how short a time the tropical ulcer can be cured. This is an all-important question, as it involves expenditure on drugs used, expenditure and time due to hospitalization, and the loss of manpower while the patient is in hospital and incapacitated.

There are two main principles in the treatment of tropical ulcer: (*a*) to check and clear the infection, and (*b*) to promote sound granulation and speedy epithelization. In evaluating the usefulness and advisability of one or another method of treatment and of drugs used, definite criteria should be applied. The drug or drugs used must clear the infection rapidly, promote healing, be easy to apply and be economically acceptable.

After many trials and experiments with different methods evolved and advised by other workers in this field, I have developed a technique which reduces the healing time by over 90%. The healing time is comparatively short—from one to four weeks—and it depends mainly on the size of the ulcer at the first examination. After the ulcer has healed there is a very little scar left and no incapacity. The numbers of patients in ulcer wards, previously overcrowded, have been reduced to a few. This treatment technique has also proved to be very satisfactory when applied by semi-skilled village aid-post orderlies, or it can be easily taught to them, and they do not need any extra equipment.

Vigorous treatment starts the moment the patient is admitted into the hospital. A patient with acute tropical ulcer receives 300,000 units of procaine penicillin by intra-

muscular injection. The same dose may be repeated on the second day if the ulcer has been very widespread, but usually the second dose may be omitted. The phagedenic slough is then removed with a dry cotton swab on an applicator. All the pockets are cleansed carefully so as to leave no gangrenous material behind. When the ulcer is clean, it bleeds freely. When the slough is adherent to the base, scissors are used to help in the cleansing. No washing of the ulcer is undertaken or ever permitted. After the ulcer has been cleansed in this way, the whole sore, the subcutaneous pockets if any and the surrounding skin are painted with 2% gentian violet solution in alcohol. A simple clean dressing of lint or gauze is then applied and the patient is sent to bed and strongly advised to remain there. The first cleansing of the ulcer and the initial painting with gentian violet are painful operations, but no anæsthetic has ever been required. On the following day the cleansing of the ulcer is repeated, and followed by painting with gentian violet. If the ulcer has been carefully and thoroughly cleansed, it is clean and shows healthy granulation tissues on the third day of treatment. Frequently there is still some serous discharge on the

FIGURE Ia.

third and even on the fourth day; but frequently this means nothing more than that the patient has taken a bath and that some of the water has run under the dressing. Swelling and tenderness are also gone by this time, and the healing and reparative process has started. The dressing is then changed to an ointment dressing. I use the following ointment, first advised by Gordzialkowsky: zinc oxide 100 parts, bismuth subgallate 100 parts, "Vaseline" 100 parts, balsam of Peru 50 parts, lanoline 50 parts, liquid paraffin sufficient to make a paste. This ointment has some advantages which are lacking in other ointments in use. Zinc oxide has the properties of being non-toxic, protective, mildly astringent, non-irritant; it seals the ulcer from outside. Bismuth subgallate has the properties of being absorbent and slightly antiseptic; it helps to keep the ulcer dry. Balsam of Peru has the property of stimulating the capillary blood supply locally and in this way promoting healthy granulation. It also stimulates resistance of the local tissues, and exercises a valuable protective action against the secondary infection. Lanoline in the base of the ointment has the property of being absorbent, as it is readily miscible with water.

When the above-mentioned substances are not readily available, zinc ointment, to which balsam of Peru is added, may be used.

The most important and also one of the most difficult tasks at this stage of the treatment is to prevent the ulcer from becoming macerated and secondarily infected. This is also the most difficult part in the whole procedure of the treatment, as it encounters resistance from the patient himself from the surrounding climatic circumstances and from the hospital staff. The patient never likes to lie in bed; he likes to wash himself frequently, although he has omitted this whilst in his village. Water is spilled all over the body, and some of the water always penetrates under the dressing, or the dressing is soaked through with water. The effect may be seen next morning when the dressing is being changed. The ulcer then has a pale and unhealthy surface macerated by water and exudate from the ulcer itself, promoted by irritation. Owing to the climatic conditions it is difficult to forbid bathing. A daily reminder that the affected leg should be kept away from the water helps but little in the long run. Medical orderlies nearly always fail to realize the importance of the proper cleansing and regular dressing which have a decisive role in the treatment of the tropical ulcer. To overcome this difficulty, I carry out the daily dressing and the initial cleansing of the ulcers myself. The daily round of the wards is prolonged for some fifteen minutes; but the patients are much better controlled, and their stay in hospital is greatly shortened.

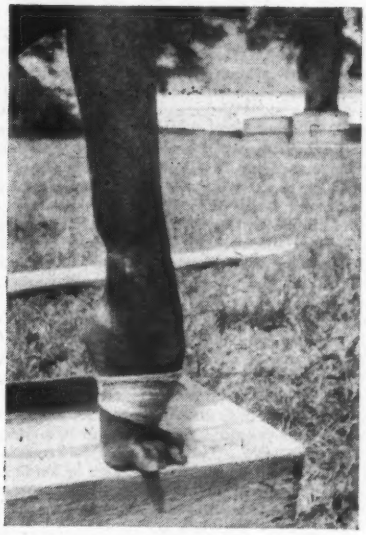

FIGURE Ib.

The treatment of chronic, secondarily infected ulcers is the same as that of acute ulcers. The secondarily infected area is cleansed with a dry cotton swab, and gentian violet is applied. When there is inflammation of the surrounding tissues, an injection of 300,000 units of procaine penicillin will help to clear the field more rapidly. After some days the ointment dressings are applied. Tropical ulcers of even many years' standing, with surrounding sclerotic scar tissues, heal in a reasonably short time. Naturally, these new scar tissues are likely to break down again if some injury is sustained in the same place. To secure a more stable result, a skin graft on such ulcers is of great help.

Prophylaxis.

An old truth, "prevention is always better than the best treatment", fits scarcely anywhere so well as in the morbidity of tropical ulcers. Personal hygiene and cleanliness of the body are the decisive factors. All, even the most minor injuries, need careful attention to avoid an infection with pathogenic organisms. A simple, clean dressing with some antiseptic solution is sufficient. On minor abrasions or cuts, cotton-wool soaked in *Tinctura Benzoini Composita* will seal the wound and protect it adequately. Education

is the most important step in prophylaxis of tropical ulcer; but for this there is a long way to go yet for the native population of New Guinea.

Summary.

Tropical ulcer, as it is seen in the Territory of New Guinea, is described. Spirochætes and fusiform bacilli are the sole causative organisms. Important predisposing causes are trauma, lack of personal hygiene, climatic conditions and impaired blood circulation. For the other predisposing causes, such as avitaminosis, malnutrition and hypoproteinæmia, there is no substantial evidence. No standard treatment is available. A comparatively simple and successful treatment, which shortens the time spent in hospital, is described.

Acknowledgement.

I wish to thank the Director of the Department of Health of the Territory of Papua and New Guinea, with whose permission this article is published. My thanks are also due to Mr. J. O'Hagan, of the Red Cross Blood Transfusion Service, Brisbane, for undertaking the serum electrophoresis in the cases investigated.

SOME SCIENTIFIC HOAXES[1]

By J. L. NEWMAN, M.D., M.R.A.C.P.,

Cornwall Geriatric Hospital, Auckland, New Zealand.

IN the world of antiques and art-collection the humbug and the faker are so notorious as to be accepted as one of the natural hazards of the game. We may deplore their activities, but after all, what they produce must be themselves works of art or they would never receive acceptance at all. Van Meegeren, the greatest genius of them all, produced a Vermeer "Disciples at Emmaus" so true to type that even the materials and pigments were such as Vermeer himself might have used. The £52,000 that it fetched may have been a fictitious price, but it embodies also its value as a pure work of art. Again, a number of Vivaldi's mostly unplayed compositions have been destroyed in an allied raid and have survived only on microfilm, so that proof of their authenticity will be for ever denied us. But would our appreciation of that superb composition "The Seasons" be any less if it was revealed that it was a bogus work photographed along with originals? In the world of science fakes are an entirely different matter, for a scientific observation is never a finite end in itself, but must be a stepping-stone to further observation or hypothesis, and if it is erroneous, then the subsequent advances become untenable and the original results are recognized as invalid. Unlike the artistic frauds, the success of the pseudo-scientist is short-lived more or less inevitably and the risks of exposure are proportionately greater; but this has not been enough on occasions to prevent the attempt. Let us turn back the files of forgotten periodicals and study again the story of two of them.

It is the presence of Sir Lionel Whitby with us today that brought to my mind the first, which occurred in March, 1930, when as a recently qualified doctor I was studying bacteriology at the Middlesex Hospital under him; and as I was the only student, I was enjoying opportunities for discussion that would not otherwise have come my way. I remember asking Dr. Whitby what he thought of an article that had just appeared in *The Lancet*, in which the author claimed to have discovered in the spinal fluid of patients with disseminated sclerosis globoid bodies, which she claimed were the cause of the disease. To me, at that time, to have an article accepted by *The Lancet* was a passport to fame, and I was the more impressed by the fact that this paper was followed by one from Sir James Purves-Stewart, describing how he had used a vaccine prepared from these bodies. But Dr. Whitby was not impressed at all, and I received an early lesson on the interpretation of other people's work that has stood me in very good stead since. It is interesting to go back now and re-read these articles with the more critical eye of experience. In reporting them I shall revert to the irritating practice of Edgar Allan Poe, and refer to the heroine of this exploit as "Miss C". After all, she may have rehabilitated herself by now, and it would not be fair for her youthful indiscretions to be dragged into the open again to confound her.

[1] Read at a meeting of The Royal Australasian College of Physicians, Auckland, August, 1956.

Miss C.'s article is a curious mixture of quite inadequate theory and apparently reasonable scientific observation. Working on the colloidal gold curve in the cerebro-spinal fluid, she found positive changes in 77% of 189 cases of disseminated sclerosis, often "in early cases before structural changes are present", though goodness knows how she knew they were not. These changes she thought must be related to the cause of the disease and not to its effects; and she went on to study some rather questionable liver function tests, whereby she inferred that the antitoxic functions of the liver were interfered with, and her preconceived ideas of an infective origin of the disease were supported. So she searched the fluids by bacteriological methods, and though she did not grow anything at first, she noted a change in the reaction of the medium when she used Hartley's broth with human serum; these changes were related directly to positivity of the colloidal gold curve. Using Barnard's technique of examining the surface of a solid culture under an oil-immersion lens, she could see "small groups or colonies of spherical bodies, some of which appear to have small refractile granules attached to them". They were very like the bovine pleuropneumonia organism; but, to quote her words, "differences of detail could be observed after careful and prolonged observation", though she does not say what they were. Contaminants were a possibility; but, to quote her again, "they develop best at different temperatures and at different times"—again she did not specify what these consisted of. The bodies could be subcultured, and she claimed that they were a living virus.

Sir James Purves-Stewart was an eager godparent to Miss C.'s child, and christened it "*spherula insularis*" in an article that followed hers. He had made a vaccine, and after tests on monkeys, had employed it in 70 cases with the following results: in eight the condition became arrested and spherulæ disappeared; in 32 it became arrested, but spherulæ were still present, although the colloidal gold curve improved; in 30, the clinical condition was uninfluenced. To judge by the stage of the disease, it was in the early cases that the results were best, but natural remissions had to be taken into account, and degeneration, once established, could not be restored.

In a second paper with Dr. Braxton-Hicks and Dr. Hocking, Sir James Purves-Stewart described the animal experiments. Ten months after intravenous or cisternal injection or both in two of seven monkeys small areas of tract degeneration were found in the cords—not necessarily disseminated sclerosis, but suggestive of it.

Like Dr. Whitby, the editor of *The Lancet* was less easily convinced. He was disappointed by the results of animal inoculation, and by the absence of any demonstration of the spherula in either cerebro-spinal fluid or brain tissue, while the demonstration of a virus in as high a proportion of cases as 93% was "almost too good to be true". If it was true, it might prove a useful diagnostic weapon. It is rather pleasant to see that even in these remote and pre-digest days, the editor thought it advisable to appeal to "the wise among whom we may include the lay press" to suspend judgement for the many months needed for confirmation.

The spherula may be said to have reached its zenith that May, when Sir James Purves-Stewart introduced it to the Royal Society of Medicine. Dr. Wilfred Harris congratulated everybody, Dr. Carlill claimed "remarkable results" from the vaccine, and no one ventured to sprinkle cold water on it.

The first discordant note was struck in February in the following year, 1931, when Sir James Purves-Stewart was forced publicly to dissociate himself from Miss C. because she had declined an invitation by the Medical Research Council to demonstrate the spherula at "Queen Square" under her own test conditions. Dr. Barnard followed suit, pointing out that his own part had consisted solely of demonstrating certain optical methods, so that he could neither claim credit nor accept responsibility for her findings. But Dr. Hicks and Dr. Hocking maintained that the spherula did exist in the cerebro-spinal fluid of disseminated sclerosis patients, and they were prepared to demonstrate it, even if they did not know what it was. They followed this up five months later, in August, by a paper in which they said that they had obtained cultures from all sorts of disease in which there was an active breaking-down of nervous tissue, and they attributed it to a flocculation phenomenon caused by the interaction of cerebro-spinal fluid and blood serum. Indeed, by this time the spherula was popping up all over the place. In France it was found in controls as well as in disseminated sclerosis subjects, and the same in Pavia. In Hungary it was found in 100 cases; and in Liverpool in 11 out of

12 cases of disseminated sclerosis, but not in controls. But the "Queen Square" investigations gave uniformly negative results. Purves-Stewart and Hocking were still finding it in all sorts of cerebro-spinal fluids except normal ones; but they were still using the vaccine and reporting arrest or clinical improvement in 20 out of 22 early cases.

Two workers in Birkenhead were also finding that the vaccine could be beneficial so long as it was given in small doses; but large doses made their patients worse in two cases. *The Lancet* was still sceptical over the absence of controls and of the lack of news about the original 70 patients, who by then had been under observation for two years. Even if the vaccine did no good, there was nothing to show that the results were any better than they might have been from simple protein shock.

The crash came at the end of that year, 1932, when Dr. Halley Stewart made what he described as a painful announcement at the Royal Society of Medicine, in which he described the whole story, and this was what had happened. In 1930, after Miss C.'s original paper, four neurologists sent her 32 specimens of spinal fluid at the request of the Medical Research Council, 15 of them from patients with disseminated sclerosis. She found the spherula in only one, and that was from a boy with chorea. She said the others must have been spoilt in transit or contaminated; but when she was asked to submit her work to a further test under her own conditions, she declined. None the less, the trustees of the Halley Stewart Institute were prepared to make further facilities available for her, and they took a house at Hampstead, which they fitted as a hospital complete with nursing staff and laboratories and with 12 beds. She was in charge of the pathology, and as she resented the presence of Dr. Stewart himself, she was left on her own with the help of an experienced technician called Lavington. The place was opened early in 1931, and by September she had obtained 121 positive results from 162 cases. She described these in a highly technical report covering 19 separate investigations, and three eminent pathologists were asked to study it. Their report was "entirely unfavourable", and one of them, Captain Douglas, noticed that three long passages were almost identical in wording with parts of three articles that had already appeared in scientific journals. So Dr. Stewart returned to the laboratory, and he and Lavington took one half of each specimen and Miss C. the other; but they could not induce her to say whether her specimens contained the virus. On October 16, they found that she had removed from her incubator all the 90 tubes that contained her "positive" cultures, and after that all the films she made were from four or five tubes she carried in the pocket of her white coat. However, before she removed her tubes, they had managed to take sub-cultures of four of them, two marked with patients' names and two with code signs, and they had managed to send them to Captain Douglas, who found that they contained pure cultures of bovine pleuropneumonia. Her explanation of this was that she was in the habit of using discarded "negative" cultures as media for growing the bovine infection without changing the labels.

And so it went on. On October 28, Stewart's incubator was found overheated with the regulator turned full on; and two days later all the control tubes were removed surreptitiously from it and dummies put there instead. The right ones were back next morning, but they had all been killed. When Miss C. was finally taxed with this, she explained that she had heated them to 60°C. for an hour and a half because she suspected that Lavington had some cultures of pleuropneumonia in the incubator, and she felt that he and Stewart were too ignorant and incompetent to handle material dangerous to themselves and the public. When Captain Douglas called on November 3 and asked for some "positive" cultures, she was sorry she had not any; but she let him take away some from Dr. Stewart's incubator, knowing that she had killed them by heat. The next day she wrote to Douglas that she was afraid a mistake had been made, as she had some cultures of pleuropneumonia in her incubator, the first time she had admitted that she had any such cultures, and she then left the building.

Still one more opportunity was offered her when she met the trustees with Sir Henry Dale and Captain Douglas. She was given sole possession of the laboratory and the right to admit 12 patients. She admitted only six, failed to obtain any "positive" cultures, and left finally before the end of the month. Halley Stewart and Lavington had examined 32 specimens of cerebro-spinal fluid and had grown nothing, though they always saw spherical bodies of various sizes and appearances, but none with the signet-ring appearance and tumbling movement demonstrated by Miss C.

As for the patients treated there, these were the results: 6% were much better; 19% were a little better; 36% were unchanged; 39% were worse. Dr. R. M. R. Walshe studied the figures and reported: "I can only conclude from your figures . . . that the patients so treated are worse off than if they had been left alone".

It is indeed a sorry story, though it is one that I am glad to say is probably unique in the annals of medical research—sad because of the misapplication of the undoubted talents of a young worker, sad because of the heartless hoax on the victims of a disease already distressing enough, and sad because of the whispered innuendoes against an older physician of repute who, it was said, ought to have realized the nature of the case, and should have refrained from turning to his own advantage a treatment so dubious. We will try to see if the conduct of either of the protagonists can be explained; but first let us consider for a moment some other cases of the pseudo-scientific hoaxer.

Only four years before the events I have related, another case ended in tragedy. Dr. Paul Kammerer was a biologist who had made a name for himself in Vienna, where he had spent his life in the Academy of Sciences working on experiments connected with the inheritance of acquired characters. In 1923 he retired, at the age of forty-three years, and two years later he was appointed to a chair in Moscow University. But before he could take it up one of the experiments on which his work depended was called in question in an alarming way. In the midwife toad, Alytes, the mating takes place on land, unlike that of most amphibians, and as a result the animals have no need of the specialized pads that develop under hormonal stimulus to enable them to clasp the female in the water. Kammerer claimed that if they were made to breed in water, these nuptial pads would develop, with asperities and pigmented skin, just as they do in other toads, and that these characters were heritable. He had demonstrated his specimens to a meeting in Cambridge. But in 1926 G. K. Noble, of New York, published a devastating paper in *Nature*. He had dissected the pads, and had found that the pigment was not in the epithelium, but was spread throughout the tissues, and was to be found in the intermuscular planes and even in the capillaries. When tested chemically for melanin, it gave none of its usual reactions; it had every appearance of Indian ink. As for the asperities on the surface, he could not confirm their presence at all, and he implied that Kammerer's photomicrographs might have been taken from some other kind of Anura, since the exact form of the spines was of no value in distinguishing many species of frogs. Dr. H. Przibram, of the Vienna Institute, contributed a following paper, in which he confirmed the observations on the nature of the pigment and the absence of asperities, which with some generosity he suggested might have become shaken off during the specimens' trip to England. But the photomicrographs alleged to have been made from this animal had some of the features of the pads of other Anura, especially Discoglossus.

But the publication of Noble's article provoked a violent reaction from the distinguished English zoologist, McBride. He wrote that he had himself seen the spines on the pads, as had "a continuous stream of critical observers", when they were exhibited at the Cambridge meeting. He had also seen another of Kammerer's artificial products, a Proteus that normally has only a rudimentary eye, but by being made to live in the light instead of the dark had been changed to one with a large eye. He suggested that Dr. Noble would be better employed in repeating Kammerer's experiments than in casting aspersions on the good faith of a fellow worker, and when he had produced anything half as wonderful as the Proteus he would be listened to with more patience.

But Dr. Noble was adamant. He stuck to his guns over the toads and suggested that Proteus was a red herring. Young ones, he said, had eyes anyway; and the fact that some should go on to develop them had no bearing on the inheritance of acquired characters or on the structure of Alytes. To this Dr. McBride replied that he had reared many of the modified males through several generations, and the acquired peculiarities became intensified in later ones. Kammerer had induced the development of the eye in Proteus and had in both cases succeeded in reviving ancestral features by reinstating the ancestral environment. It was the work of a skilled experimenter, not of a clumsy trickster.

But by the time McBride's last letter was published, tragedy had come upon the scene. Kammerer had admitted that the pigmentation was faked, though he denied that he himself had

done it. He went up onto a hillside near Vienna and shot himself, leaving a note to say that it was too late to begin all over again. He was forty-six years old, and on the threshold of a professorship in a foreign land. Had he indeed faked those pads? Or had some other worker in his laboratory, perhaps anxious to please the Chief, done the thing to provide the evidence that he knew was wanted? And what of all Kammerer's previous work, on Proteus and other animals, that had been the basis of his international reputation? Was that faked too? Most of his investigations had been carried out on salamanders. One kind, *S. atra*, normally reproduces on land, and produces two young with no gills: the other kind, *S. maculosa*, produces 20 aquatic tadpoles with gills, which then metamorphose. When *S. atra* was kept in warm, moist conditions it produced increasing numbers of aquatic larvæ like *S. maculosa*. *S. maculosa*, if kept in dry surroundings, finished by producing terrestrial young with no gills. The newly acquired habit induced by changed conditions was inherited, and hence a Lamarckian effect was produced (Fothergill). It would not have been difficult to substitute one kind of salamander larva for the other. Nor would it have been difficult to make a similar substitution in another of his experiments, in which he claimed to have induced inheritable colour changes by rearing yellow salamanders in a black box and black ones in a yellow box. In another of his experiments, which stretches our credulity to the utmost, he had grafted the ovary of one kind of salamander into another, and claimed that the offspring that eventually resulted bore the characters of the adoptive mother. All Huxley (1924) has to say of it is: "An unfortunate suspicion rests on Kammerer's work and his results on salamanders have not been confirmed by Herbst."

No discussion on pseudo-scientific frauds would be complete without mention of what is at present the most celebrated of them all, the Piltdown skull. It will still be fresh in the minds of many of you, especially those who have read that fascinating book, "The Piltdown Forgery", by J. S. Weiner, but I hope I may be forgiven for a brief sketch of it.

Charles Dawson was a small-town solicitor at Uckfield, with antiquarian and scientific interests. He was an indefatigable collector of flints, and had made an important discovery in the early 1890's of the teeth of "plagiaulax", a mesozoic mammal of earlier date than any hitherto known. But in 1893 he had explored some caves in the gravel beds at Lavant, and had done it so amateurishly that valuable evidence of their history was lost, as were the caves themselves shortly afterwards—a small matter that was of personal interest to me, as I built a house on the supposed site of one of them years later, and surprised the insurance company by taking out a policy against its disappearance.

Dawson had gone on to publish a "History of Hastings Castle", which was later recognized to be largely plagiarized, and to discover an outflow of natural gas at Heathfield, and several new dinosaurs. His reputation as a geologist was established in London; but in Hastings circles he was regarded with a suspicion that gave way to actual dislike when he bought the headquarters of the Sussex Archæological Society over the heads of the Society, of which he was himself a leading member.

Such was the man who in 1912 announced, in conjunction with Mr. (later Sir) Arthur Smith Woodward, the Keeper of Geology at the British Museum, the discovery of cranial fragments which he identified from geological surroundings as being earlier than any hitherto found in Europe. These fragments had been collected from a small gravel pit over a period of years, the first by Dawson alone and the later ones by associates among whom was Woodward himself. Only Dawson's word guaranteed the bona fides of the first; but the later ones, and especially a piece of mandible of ape-like characters, were found at levels that could be identified by their relation to coliths—the earliest kind of flint tool—and the remains of prehistoric rhinoceros and planifons elephant. The "dawn man" fulfilled "evolutionary expectations in his form, in his age, in his tools, and in the character of the animals of his time" (Weiner, 1955).

In spite of what seemed at the time convincing evidence, largely perhaps because of the eminent names associated with it, including those of Elliot-Smith and Arthur Keith, there were always those who believed that a jaw with such undoubtedly simian characters could not have belonged to a human skull: and without the evidence of the jaw, Piltdown man's claims became tenuous. In fact, by 1953 discoveries of earlier remains elsewhere, in China, Java and Rhodesia, had indicated that human ancestors had not developed on anything like the evolutionary lines suggested by Piltdown man, and the stage was set for the brilliant review by Weiner and Oakley. You will find all the scientific evidence in Weiner's book. There he tells how the fluorine content showed that the skull and jaw were of different dates, and how the nitrogen content showed that the jaw was a recent specimen; how the teeth were shown to have been artifically ground down and coloured with Vandyke brown; how the bony fragments and the flint tools were shown to be stained artificially with chromium and iron; how the elephant tooth was identified by its radioactivity as a North African specimen; and much else besides. Piltdown man was left without a leg to stand on, though from Dawson's character we can imagine that one might have been planted in the gravel pit if the need had been foreseen.

Comment.

If we are to analyse these three frauds, we must consider three aspects of them, two of them having obviously common ground, while in the third the motive of the fraud is complex. Was there a common thread running through all three? Or is there any basis which might lead someone else to repeat their attempts? Of Kammerer it is difficult to speak with any degree of certainty. There was not *a priori* a reason why most of his work on salamanders should not have been genuine, however reluctant one may be to accept his conclusions on transplanted ovaries. On the other hand, he could have been a humbug. It would have been easy enough to substitute yellow salamanders for black or lung-breathers for tadpoles. Did he mix bogus work—these experiments and those on Alytes—with genuine—the changes in Proteus which could not have been faked? Or was he an honest man who drew the wrong conclusions because, like McBride, he approached them with an uncritical mind? In that case, the Alytes must have been planted on him by someone else.

If, as he thought, he had established the success of one faked experiment, it would have been natural for someone with a warped mind to think it was all too easy, as Miss C. seems to have done, and to go on to further fakes with the idea of bolstering up what had already been done—making assurance doubly sure, as Dawson did when he claimed the discovery of a second eoanthropus from a site adjacent to Piltdown. Or the other hand, Kammerer's behaviour in putting the notorious specimen of Alytes at the disposal of his critics was not the act of a guilty man. But then, neither was Neville George Heath's, when he had murdered a woman in a London flat and then wrote to Scotland Yard over his own name, drawing attention to his association with the crime. And if Kammerer had himself been the victim of a hoax which threw doubt on all his life's work just as he was about to step into an important post in a foreign land, he might well have felt he could not face it and have taken the way out by suicide.

In the cases of Dawson and Miss C., we have undoubtedly a carefully planned and skilfully carried out series of deceptions. There is not much difference between putting a foreign organism into a culture tube and putting a Tunisian elephant's tooth into a Sussex gravel pit. Yet for both, whatever satisfaction they might get from success, exposure—and exposure was a very real risk—meant the end of a burning ambition to secure a niche in the façades of pathology and archæology, wherein they could be seen and admired by all men, outside as well as inside their own particular group. This readiness to risk the substance for the shadow is strongly suggestive of Mr. Anthony Hawke's definition of a psychopath as "a person who takes a short-term view: a person who does what he feels like doing at the moment without any thought of what the consequences may be" (Critchley, 1955). We all know them and we have all suffered from them—brilliant at times, utterly untruthful and unpredictable, ranging in their activities from people like Neville Heath to the malicious pests who make a hospital ward a misery for their fellow patients. Surely it must be this sort of a psychological urge that drives them on, rather than the simple desire for revenge, postulated by Mrs. Sonia Cole (1955) for that erratic genius Van Meegeren, and some of the other frauds in her book "Counterfeit".

Turning now to the common features of these three cases, we find that they are two—the climate of scientific opinion at the time, which allowed the frauds of flourish, and the appearance in each case of a well-known and influential authority to lend his support to them. The background of Darwinism to Kammerer and Dawson is obvious. The contest between the

inheritance of acquired characters and pure natural selection is not yet settled and was more acute thirty years ago than it is today. The Lamarckians were simply waiting open-armed for just the evidence that Kammerer purported to provide, and in Professor McBride they found a doughty champion whose scientific discrimination could not resist the tempting morsel. I have not found his final views on Alytes; but his faith in Kammerer remained unshaken, and in 1932 he wrote as follows of some of his work on the production of changes in the characters of baby salamanders: "We consider these results of Kammerer and Durkhen literally epoch-making for the theory of evolution in zoology." McBride accepted the evidence of Alytes, not because he had subjected it to critical analysis, but simply because he wanted to accept it, and having accepted it, he was still too wedded to the theory and too deeply committed by his acceptance to be able to attach due weight to Noble's exposure. In the same way, the Piltdown forgery was worked at just the right time. The discovery of the missing link could be guaranteed to hit the headlines, no less than to bring to their feet all the anthropologists, the palæontologists, and even the ecclesiastics, to whom the final proof of Darwinian evolution as applied to man was of vital interest. Eoanthropus, half man and half ape, was just what popular imagination demanded, though the combination of man's calvarium and ape's jaw was a bit of a pill for even the most enthusiastic to swallow, even if swallow it most of them did. Again there was the eminent Arthur Smith Woodward to champion the discovery. He had not such a prejudiced outlook as had McBride, but he was obviously an easy victim, and like McBride he was unable to scrutinize the evidence with a critical eye because of his implicit confidence in the perpetrator of the fraud. Kammerer's work, up to the time of the Alytes incident, had commanded respect, and however much Dawson may have been suspect in his own immediate circle, he was known in London as the reputable finder of *Plagiaulax Dawsoni*. It must have been this that led even authorities of the calibre of Sir Arthur Keith to accept his dating of the skull fragments on nothing but his own uncorroborated evidence. In 1948 Keith wrote as follows: "If we could get rid of the Piltdown fossil fragments we should greatly simplify the problem of human evolution." But he rejected Dr. F. Weidenreich's advice—"Eoanthropus should be erased from the list of human fossils. It is the artificial combination of a modern-human brain case with orang-outang-like mandible and teeth". And the reason why he rejected such an obvious criticism was—to quote Keith again: "If we are convinced that evolution is the true method of creation and that man and anthropoid have been derived from a common ancestry, what is more probable than that we should find early human forms in which anthropoid and human features are combined?"

To turn to disseminated sclerosis, there was—and is—a tremendous and widespread desire to establish its ætiology. Such a discovery might not only pave the way to the relief of a common and dreadful malady, it would open a new chapter of neuropathology in relation to demyelinating diseases. As for Sir James Purves-Stewart, I think a comparison with Smith, Woodward and McBride should help us to appreciate his motives and free him from any suspicion of having cashed in on the vaccine before anyone got a chance to show that it was worthless. He had been nurtured in the heyday of the bacteriological era; he must have been waiting for the demonstration of a micro-organism in a disease which was commonly believed to be infective, and as he had seen the rise of vaccines in treatment, what could be more natural than for him to regard a vaccine as the logical and immediate sequel of the discovery? Should we today be any more critical of a new antibiotic directed against the staphylococcus if we thought we could be the first to take advantage of it? Of course it was an injudicious thing to do; but I believe myself that all three of our experts had the same basic background, and that Sir James Purves-Stewart was merely unfortunate in having turned it to his own personal advantage.

I have spoken of the uncritical acceptance of unsatisfactory scientific evidence. The reverse may be equally dangerous—the rejection, on emotional grounds, of evidence that would otherwise appear convincing. I think we have had an example of this lately here in connexion with the fluoridation of the city's water. One of the City Fathers wrote to an eminent Australian professor for his opinion, and was treated, not so much to a reasoned exposure of misleading evidence, as to a passionate diatribe against "the sacrifice of reason" involved in letting a municipal authority add things to what should be a natural article for human consumption. I would rather see a psychologist than a physiologist tell me what is reasonable behaviour, especially when the physiologist's opinions are distorted by an otherwise laudable preference for uncontaminated foods grown on natural media. There is still plenty of room alongside the Sir Arthurs and Sir Jameses.

The opinions so unfortunately adopted by these eminent champions are not without a bearing on ourselves. We may not find ourselves exactly in their situations; but every one of us is in something of the same position when he is subjected to the pressure of high-powered modern salesmanship, and the uncritical acceptance of some of the much-vaunted remedies of the last few years comes to mind. Does any of us suppose, for instance, that psychiatric elucidation or the supporting ministrations of religious faith can be short-circuited and the deep-seated agonies of the human soul really relieved by a bottle of ataraxic tablets? The angler may be never so careful in his choice of a fly, and incredibly expert in casting it in the right place; but in the final analysis his success depends on just one thing—the presence, waiting open-mouthed for it, of some poor fish.

References.

COLE, S. (1955), "Counterfeit", Murray, London.

CRITCHLEY, McD. (1955), "Famous Trials", Penguin Books, London: 89.

FOTHERGILL, P. B. (1952), "Historic Aspects of Organic Evolution", Hollis & Carter, London: 258.

HUXLEY, J. (1942), "Evolution: The Modern Synthesis", Allen & Unwin, London: 458.

KEITH, A. (1948), "A New Theory of Evolution", Watts, London: 229.

McBRIDE, E. (1926), *Nature*, 2: 264.

McBRIDE, E. (1932), in "Evolution in the Light of Modern Knowledge", Blakie, London: 239.

NOBLE, G. K. (1926), *Nature*, 2: 209.

PURVES-STEWART, J. (1930), "A Specific Vaccine Treatment in Disseminated Sclerosis", *Lancet*, 1: 560.

STEWART, H. (1932), *Brit. M. J.*, 2: 326.

WEINER, J. J. (1955), "The Piltdown Forgery", Oxford University Press: 7

PEPSINIZED GRASS POLLEN IN THE TREATMENT OF HAY-FEVER: A FURTHER REPORT.

By R. S. COLTON AND H. N. ROBSON,

Department of Medicine, University of Adelaide, Adelaide.

Good results have been claimed by Piper (1955, 1956) in the treatment of hay-fever with the use of a pepsinized rye grass pollen preparation as a desensitizing agent.

The results of a trial of this method were reported by us in 1956; some relief appeared to have been obtained in 72% of the 253 cases treated. However, this trial was not controlled and it was thought that further tests should be made.

This paper reports the results of a further trial, in which controls were used, and from which more definite conclusions may be drawn.

Methods.

About 60 volunteers were obtained from an industrial undertaking near Adelaide. Only those with a definite history of spring hay-fever were accepted, and it was finally possible to treat and fully assess 44 patients. The factory used in this experiment was not used for the previous experiment the year before, and none of the patients had ever received desensitization treatment.

In the preliminary interview a brief history was taken of the duration of symptoms and their severity. Scratch tests were not made on this occasion, as it was considered that a clear-cut history was of more value and made skin tests unnecessary.

The patients were divided into three groups by the severity of their symptoms. In Group I were those with most severe symptoms usually necessitating some time away from work during the season; there were 15 of these. Group II contained those with moderately severe symptoms (18), and Group III those who considered that their symptoms in the spring were of nuisance value only (11).

Each of the three groups was then divided into two approximately equal subgroups, one of which received the pollen solution and the other the control solution. The control solution used was papaverine. This produced a similar weal and flare to the pollen.

The technique was as previously described by Piper (1955). Six intradermal injections were given at the rate of two a week. The initial dose of pollen was 0·01 cubic centimetre of a solution originally containing, prior to protein digestion, the equivalent of 10,000 Noon units to the cubic centimetre.

All the members of each subgroup were as far as possible treated together, so that approximately equal numbers of control and pollen solutions were given each time. It was not a "double blind" trial in that the operator knew which solution he was using.

Injections were begun in the first week of September, and most of the cases were completed by mid-October. All treatment was finished by the first week in November.

Assessment.

Subjects were asked about their symptoms during the treatment, and were reviewed a month after its completion. Many of the earlier patients treated were reviewed again at the end of their second month also, and the inquiry was thus carried on to the first week of December. It was considered that the peak of the season occurred in the last half of October and the first few weeks of November.

An estimate of symptomatic relief was asked for, and this was expressed as a percentage. If the results were conflicting at the conclusion of the experiment in any one case, this was indicated in the tables. Thus it could happen that a patient considered he was not better at the end of the treatment and was 75% better during the next month. Only those claiming 50% relief or over were classified as having had any significant relief. None of those who claimed relief had received any significant antihistamine pill treatment. There were no systemic reactions in the 22 patients who were given the pollen solution.

Results.

The results are shown in Tables I, II and III. In Table I, referring to those with the most severe symptoms, only two out of eight of the pollen group claimed significant relief, and in neither of these was any relief claimed during the injections. Among the corresponding controls, six out of seven claimed some relief. One patient in this latter group claimed that she had never had a better year since the start of her hay-fever six years earlier. Another in the control group said that he had almost complete relief during and after the course, and that he had hardly had any of the symptoms from which he invariably suffered for six weeks.

In Table II, five out of nine of the pollen group had relief, and six out of nine of the controls. In Table III it is seen that four out of five of the pollen-treated group and three out of six of the controls experienced significant relief.

The total results show that 11 of 22 (50%) who received the pollen claimed significant relief, and 15 out of 22 (68%) in the control series.

Conclusion.

It is thought that the results of this experiment should be published, if only to illustrate once again the caution that is necessary in the interpretation of the results of treatment in such a condition as hay-fever.

Depending on a purely subjective analysis of symptoms, as these results do, makes a control series essential for adequate interpretation. It is appreciated that the numbers used in this series were small, and dogmatic conclusions cannot be drawn. But it is interesting to find that papaverine, with no known allergic action, can produce comparable, in fact better, results than the pollen solution when similar methods of assessment to those in the previous investigations are used.

A total of 15 out of 22 (68%) of the control series claimed some significant improvement during or after the course. It is considered that the method and criterion used in estimating subjective improvement could well be altered. If no improvement occurs during the course, then it is surely open to considerable doubt, if improvement occurs later, that the injections were responsible. Also, if the figure of 50% is eliminated and significant improvement is taken as only 75% or over, then perhaps a more accurate picture will be obtained.

TABLE I.
Group I.

Pollen-Treated.	Improvement.	Control Group.	Improvement.
1	Nil.	1	Nil.
2	Nil.		50%
3	Nil.	2	Nil.
	75%	3	75%
4	Nil.	4	Nil.
5	Nil.		50%
6	Nil.	5	90%
7	Nil.	6	50%
8	75%	7	75%

TABLE II.
Group II.

Pollen-Treated.	Improvement.	Control Group.	Improvement.
1	Nil.	1	Nil.
	50%		50%
2	90%	2	90%
3	Nil.	3	Nil.
4	50%	4	75%
5	75%	5	Nil.
6	Nil.		75%
	50%	6	Nil.
7	Nil.		50%
8	Nil.	7	Nil.
9	Nil.	8	Nil.
		9	50%

If the results are analysed again, with the use of this stricter assessment of improvement, it is found that essentially similar results are obtained in both series. Five out of 22 pollen-treated patients (23%) and six out of 22 of controls (27%) were improved.

TABLE III.
Group III.

Pollen-Treated.	Improvement.	Control Group.	Improvement.
1	Nil.	1	Nil.
	50%		50%
2	75%	2	75%
3	90%	3	Nil.
4	Nil.		50%
5	50%	4	Nil.
		5	Nil.
		6	Nil.

If this method is used again in an analysis of the most severe cases, only one patient out of eight who were treated with the pollen solution was improved.

Summary.

The results of a small controlled experiment in the use of pepsinized rye grass pollen in the treatment of spring hay-fever are presented. In the original method of assessment, as used in previous reports, 68% of the controls and 50% of the pollen-treated patients showed significant improvement. With a stricter method of assessment, only

27% of the controls and 22% of those who received the pollen preparation were improved.

Acknowledgements.

We should like to express gratitude for the generous cooperation of the management and personnel of Philips Electrical Industries (Australia, Proprietary, Limited) in this work, and for financial support from the Mortlock Research Fund, University of Adelaide.

References.

COLTON, R. S., and ROBSON, H. N. (1956), "Pepsinized Grass Pollen in the Treatment of Hay Fever", M. J. AUSTRALIA, 2: 408.

PIPER, C. T. (1955), "Hay Fever and the General Practitioner", M. J. AUSTRALIA, 1: 303.

PIPER, C. T. (1956), "Protein Digests in the Treatment of Allergic Disease", M. J. AUSTRALIA, 2: 4.

THE USE OF "MEGIMIDE" AS A CONVULSIVE ACTIVATOR IN ELECTROENCEPHALOGRAPHY FOR THE DIAGNOSIS OF EPILEPSY.

By K. ANDERMANN, M.B., B.S.,

Electroencephalographic Department, Mental Hospital, Mont Park, Victoria.

PROFESSOR F. H. SHAW found that "Megimide"[1] (beta-ethyl beta-methyl glutaramide) was an effective antidote for barbiturates and of considerable help in the treatment of barbiturate poisoning, and that large amounts of megimide injected in laboratory animals produced severe convulsions (Shaw, 1954). These observations induced various French workers to use megimide, instead of the customary "Metrazol", as an epileptic activator in electroencephalography for the diagnosis of epilepsy. They reported that megimide could be successfully used for this purpose, and that it was in several respects even superior to "Metrazol". It was decided to try to confirm these findings, and in addition to test the convulsive threshold of known epileptics to see if there was any difference between latent epileptics and non-epileptics. Megimide, instead of "Metrazol", was accordingly used as a routine agent for activation of epilepsy in the Electroencephalographic Department at the Mental Hospital, Mont Park, Victoria, over a period of six months. The observations made are described in this article.

Method.

Megimide was supplied to us by Professor Shaw in the form of sterile aqueous solution at a concentration of 5%. The drug was tested on 30 patients who were referred to us, with their clinical history, by the various mental hospitals and psychiatric clinics of the Victorian Mental Hygiene Department. Eight of these patients were known to suffer habitually from major seizures, eight had some sort of physical "fits" thought possibly to be epileptic in character, 12 suffered from paroxysmal psychological disorders, one was suffering from general paralysis of the insane, and one had no history remotely suggestive of epilepsy.

To start with, we took electroencephalographic recordings under standardized conditions with the patients in the resting state. Then we recorded electroencephalographic tracings during hyperventilation and photic stimulation. If, after the latter procedure, the electroencephalogram did not show any dysrhythmia, we eventually gave a combination of photic stimulation and megimide activation. Using this method suggested by the French workers, we injected rapidly, within fifteen seconds, six cubic centimetres of the megimide solution intravenously. Then we placed a stroboscope before the closed eyes of the patient and applied intermittent bursts of flicker of strong light. If after this procedure the electroencephalogram did not show any convulsive abnormality, a further two cubic centimetres of megimide were injected and new bursts of flicker given. This last procedure was repeated again and again until the electroencephalogram recorded synchronous spikes in all scalp regions, usually followed by a slow wave, or until other forms of seizure patterns occurred. We did not intend initially to use more than 20 cubic centimetres of the megimide solution, as we wished to see how far this dosage would produce activation of epileptic rhythms. On several occasions we also used continuous light flicker for longer than one minute, during which period the flicker frequency was gradually decreased in a range from 23 to 2 cycles per second. We recorded the quantity of megimide solution which produced the first seizure patterns or larval seizure patterns, the characteristics of the latter, and the clinical state of the patient during the activation. From the quantity of megimide injected and from the weight of the patient we calculated the critical megimide body concentration in terms of milligrammes of megimide per kilogram of body weight.

Four patients were given "Sodium Pentothal" intravenously in order to prevent a clinical, megimide-produced, major seizure which we suspected was impending, judging by the frequently and rhythmically recurring electroencephalographic seizure patterns. On one occasion we were able to compare the effect of megimide with that of "Metrazol" in the same patient, and on another occasion the effect of megimide with natural sleep.

The therapeutic clinical effect of anticonvulsive treatment on those patients who exhibited seizure patterns in their electroencephalogram could be established in eight cases.

Analysis and Discussion of Findings.

The observed findings are set out in Table I.

Material, Experimental Procedure and Controls.

In view of the fact that we were not originally intending to inject more than 20 cubic centimetres of the megimide solution, it is possible that a few patients with a mild epileptic tendency did not show any seizure patterns in their electroencephalographic tracings. However, such cases could not have been many, as 22 out of the 30 patients examined did show seizure patterns in their electroencephalogram.

The population tested with megimide was not drawn from a "normal epileptic population", but from a psychiatric population supplied by mental hospitals and psychiatric clinics. I think that this was an advantage for the purpose of this investigation, as in this way a greater variety of unusual forms of epilepsy could be tested.

In four patients, forty to eighty seconds after the initial rapid injection of the megimide solution, "spurious" bursts of waves or even seizure patterns appeared in the electroencephalogram; but these disappeared after a further eighty seconds. This phenomenon suggested to us that about sixty seconds after the injection the megimide reached an abnormally high concentration in the brain before it had a chance to mix homogeneously in the whole blood. This inference seemed also to be borne out by observation of other patients who received "Sodium Pentothal" intravenously; in these, the characteristic fast activity in the electroencephalograms appeared forty to sixty seconds after the injection and disappeared after a further 100 seconds. The phenomenon probably also explains the unexpected occurrence of megimide-induced major seizures in two of our patients (Cases 8 and 30) after the too-rapid injection of the drug. This complication of "spurious" wave bursts, possibly leading to incorrect diagnostic inferences, as well as to the occurrence of accidental major seizures, could probably have been avoided if the megimide solution had been injected at a slower rate.

The seizure patterns in the electroencephalogram were not obtained by megimide alone, but by a combination of megimide with photic stimulation. As we used the same lamp for all patients of this series, the electroencephalographic tracings can be validly compared.

[1] "Megimide" is the proprietary name adopted by Nicholas Proprietary Limited for bemegride.

TABLE I.

Case Number.	Sex.	Age. (Years.)	Clinical Status.	Megimide. (Cubic Centimetres.)	Body Weight. (Pounds.)	Megimide in Milligrammes per Kilogram of Body Weight.	Electroencephalographic Findings Before Megimide.	Electroencephalographic Findings after Megimide.		Clinical Effects of Megimide.	Effect of Anti-Convulsants.
								Seizure Patterns.	Frontal Theta Waves.		
1	M.	52	Chronic alcoholic; malingering; reported nocturnal tongue-biting and incontinence of urine and fæces.	26	154	1·9	Some frontal theta and sharp waves.	Nil; frontal short spikes.	Slow, high voltage.	Nil.	—
2	M.	38	Impulsive and aggressive episodes, with insight.	30	182	1·8	Some frontal theta waves.	Nil.	Few.	Nil.	—
3	M.	46	General paralysis of the insane; major seizure three months earlier.	20	120	2·0	Slow waves in prefrontal and left parietal regions.	Bursts of frontal high voltage slow waves.	Slow waves of higher voltage.	Nil.	—
4	M.	17	Blackouts; hallucinatory voices; behaviour disorder.	20	145	1·5	Few scattered slow frontal waves.	Nil.	Some increase.	Nil.	—
5	M.	15	Temper tantrums; violent aggressive behaviour.	3	120	0·3	Right frontal spikes and scattered "*petit mal* variants".	Poly-spike wave seizure pattern.	Nil.	Twitching.	—
6	F.	52	"Fits" associated with menses.	14	173	1·0	Few theta waves; three different alpha frequencies.	Nil.	Many, spreading posteriorly.	Nil.	—
7	M.	43	Epileptic; alcoholic.	8	144	0·7	Prefrontal and frontal spikes and theta waves.	Myoclonic seizure pattern.	Increased.	Nil.	—
8	F.	17	Episodes of clouded consciousness; schizophrenia; behaviour disorder.	12	101	1·3	Low voltage theta waves in all regions.	(i) Myoclonic seizure pattern; (ii) major seizure pattern.	Low voltage theta waves.	Major seizure.	No improvement.
9	M.	15	Periodic restlessness; behaviour disorder.	18	112	1·8	Frontal sharp waves and theta waves and "*petit mal* variants".	Larval spike and wave seizure pattern.	Increased.	Nil.	Some improvement.
10	F.	18	Paroxysmal behaviour disorder; mental deficiency.	6	142	0·5	Low voltage slow waves dominate all regions.	Larval spike and wave seizure pattern.	As before.	Nil.	Improved.
11	F.	20	Delayed insulin-coma; schizophrenia; no history of fits.	20	108	2·1	Occipital sharp waves.	Nil.	Theta waves appear.	Nil.	—
12	M.	31	"Fits"; behaviour disorder.	10	136	0·8	Some frontal theta waves; sharp alpha waves in left temporal region.	Myoclonic type seizure pattern.	Increased.	Twitching.	—
13	M.	40	Major seizure nine years earlier when suffering from meningitis.	30	126	2·7	Prefrontal and frontal theta waves; spikes in right frontal region.	Nil.	Increase; right frontal spikes.	Nil.	—
14	F.	17	Episodic furors.	10	120	1·2	Frontal theta waves; temporal spikes and waves.	(i) Slow wave seizure pattern (ii) temporal high voltage slow waves.	Present.	Nil.	Improved.
15	M.	36	Major seizures of recent onset; hysterical paralysis of legs.	16	120	0·8	Few frontal theta waves.	Spike-and-wave (three cycles per second) seizure pattern.	Some.	Nil.	—
16	M.	38	Psychopathy; headaches; hydrocephalus.	20	184	1·2	Frontal theta waves; double alpha frequencies.	Nil; sharp alpha waves.	Increased.	Nil.	—

TABLE 1.—*Continued.*

Case Number.	Sex.	Age. (Years.)	Clinical Status.	Megimide. (Cubic Centimetres.)	Body Weight. (Pounds.)	Megimide in Milligrammes per Kilogram of Body Weight.	Electroencephalographic Findings Before Megimide.	Electroencephalographic Findings after Megimide.		Clinical Effect of Megimide.	Effect of Anti-Convulsants.
								Seizure Patterns.	Frontal Theta Waves.		
17	M.	38	"Fits" involving sudden loss of contact with reality and smell of burning.	14	148	1·0	Few frontal theta waves; double alpha frequency.	Synchronous spikes.	Increased.	Twitching of right arm and face; smell of crackers.	Improved.
18	M.	16	Epileptic; myoclonic; aggressive-paranoid.	22	175	1·3	Prefrontal, frontal and occipital theta waves.	Poly-spike wave bursts in frontal and "*petit mal* variants" in occipital regions.	Slightly increased.	Nil.	—
19	M.	48	? Epileptic coma in epileptic.	20	165	1·3	Slow frontal waves.	Synchronous spikes in left hemisphere and right occipital region.	Slightly increased and spreading posteriorly.	Nil.	—
20	M.	23	Deteriorating schizophrenia with compulsive features.	16	170	1·1	Few frontal theta waves.	Poly-spike wave seizure pattern.	Present.	Dry taste in mouth.	No improvement.
21	M.	48	? Schizophrenia, ? organic syndrome.	20	174	1·3	Some frontal theta waves, spikes and "*petit mal* variants".	Nil; frontal and temporal "*petit mal* variants".	Increased.	Nil.	—
22	F.	31	Major epilepsy of recent onset; haemoglobin value, 56%; depression; immaturity.	6	90	0·8	Theta waves found in all regions.	Eight-cycles-per-second waves; high voltage seizure patterns.	Not increased.	Nil.	—
23	F.	36	Epileptiform seizures seven years previously; now atypical ? hysterical fits.	6	138	0·3	Theta waves found in all regions.	Poly-spike wave seizure pattern.	Slightly increased.	Twitching.	—
24	F.	42	Major seizures for six months; chronic schizophrenia.	8	154	0·6	Frequent frontal theta waves.	High voltage seizure pattern.	Slightly increased.	Nil.	—
25	M.	20	Behaviour disorder; psychopathy; alcoholism.	8	163	0·6	Theta waves found in all regions.	Six to seven cycles per second theta wave larval seizure pattern.	Increased.	Nil.	Improved.
26	F.	39	"Stiff turns" every few months; ? epilepsy.	14	92	1·7	Theta waves found in all regions.	Myoclonic type of seizure pattern.	Slightly increased.	Queer sensation in stomach.	—
27	M.	22	Recurrence of nocturnal major seizures after a break of five years.	18	162	1·2	Theta waves found in all regions.	Myoclonic type of seizure pattern.	Increased.	Nil.	—
28	F.	56	Epileptic seizures; paranoid schizophrenia.	14	130	1·2	High voltage frontal theta waves.	(i) Poly-spike wave seizure pattern; (ii) slow wave seizure pattern.	Slightly increased.	Nil.	—
29	M.	23	"Fainting" attacks; paranoid schizophrenia; ? epilepsy.	20	143	1·5	Diffuse theta and delta waves; left Rolandic "phantom spike and wave".	Bursts of spike and wave in both Rolandic regions.	Slightly increased.	Nil.	—
30	F.	42	"Turns"; confusion; chronic schizophrenia.	20	134	1·7	Some frontal theta waves.	(i) Myoclonic type of seizure pattern; (ii) major seizure pattern.	Increased.	Major seizure.	—

Megimide Used in Electroencephalography for the Diagnosis of Epilepsy.

In the use of megimide as an activator of the electroencephalogram in the diagnosis of epilepsy, let us first consider the concentrations necessary for the production of seizure patterns, or larval seizure patterns, in the electroencephalograms of epileptics as contrasted with non-epileptics. Twenty-two of the 30 psychiatric patients tested had convulsive electroencephalographic tracings, under the combined effect of megimide and photic stimulation, which were not present without this form of activation. The body megimide concentrations required for the production of these seizure patterns varied from less than 0·8 to 1·8 milligrammes per kilogram (mean, 1·0 milligramme per kilogram). Eight patients had a history of clinically diagnosed habitual major seizures and could therefore be classified as "epileptics". All of them exhibited seizure patterns with megimide at concentrations of 0·3 to 1·3 milligrammes per kilogram (mean, 0·9 milligramme per kilogram). Ten patients, who were all suffering from paroxysmal psychological disorders, exhibited seizure patterns with megimide, in spite of the absence of a history of major seizures. The body megimide concentration required for the production of electroencephalographic seizure patterns varied from 0·3 to 1·8 milligrammes per kilogram (mean, 1·0 milligramme per kilogram). The suspicion that these episodes of paroxysmal psychological disorder were of the nature of epileptic equivalents was confirmed by the clinical improvement of four out of seven patients after anticonvulsive treatment. One patient (Case 14), with a history of violent furors, showed in the resting electroencephalogram of one temporal region "*petit mal* variants" suggestive of an epileptogenic temporal focus. Megimide activation produced continuous high-voltage slow-wave activity in the same temporal area. This patient improved considerably with anticonvulsive treatment. This case suggests that megimide may be of definite use in showing up epileptogenic foci. The characteristics of the seizure patterns of epileptics suffering from major seizures were as follows: (*a*) poly-spike-wave seizure patterns, four patients; (*b*) discrete synchronous spike-and-wave in all regions, three patients; (*c*) wave-and-spike seizure patterns, one patient; (*d*) theta-wave seizure patterns, one patient. In patients suffering from paroxysmal psychological disorders, the seizure patterns encountered were as follows: (*a*) poly-spike-wave seizure patterns, three patients; (*b*) discrete synchronous spike-and-wave seizure patterns, two patients; (*c*) larval wave-and-spike seizure patterns, one patient; (*d*) theta-wave and delta-wave seizure patterns, four patients. This demonstrates that megimide can activate practically all known forms of seizure patterns in the electroencephalogram. If we restrict the survey to the four patients with theta-wave and delta-wave seizure patterns who were likely to suffer from psychomotor epilepsy, we find that they required body megimide concentrations varying from 0·6 to more than 1·8 milligrammes per kilogram (mean, 1·3 milligrammes per kilogram). These figures suggest that possibly some patients with psychomotor epilepsy require a little more megimide than ordinary epileptic patients, and occasionally considerably more, which confirms the observations of the French workers.

The control figures for the megimide concentrations necessary to produce electroencephalogram seizure patterns in non-epileptics are, unfortunately, not available in this investigation. Nevertheless, some figures supplied in this series are helpful in showing that they are higher than those of epileptics. One patient (Case 11), who was a non-epileptic, received 2·1 milligrammes per kilogram of megimide without showing any electroencephalographic seizure patterns. Another patient (Case 13), who had suffered from meningitis nine years previously, when he had one major seizure, and had had none since, did not show any seizure patterns in spite of the administration of 2·7 milligrammes per kilogram of megimide. A third patient, who, during an active stage of syphilitic infection of the cortex, suffered from a major seizure, and had had none before, received 2·0 milligrammes per kilogram of megimide without the production of any seizure patterns in his electroencephalogram. The French workers report that they had to inject more than 50 cubic centimetres, and in one case more than 135 cubic centimetres, of the megimide solution before seizure patterns turned up in the electroencephalogram. Unfortunately, they do not give the corresponding figures in terms of megimide concentration in the body. If the average weight of a person is taken as being 60 kilograms, the corresponding body megimide concentrations work out at 4·1 and 11·3 milligrammes per kilogram respectively.

From the foregoing, it may be stated that all known epileptics, suffering habitually from major seizures, showed, with megimide activation, seizure patterns in their electroencephalograms at concentrations varying from 0·3 to 1·3 milligrammes per kilogram (mean, 0·9 milligramme per kilogram). Ten patients suffering from paroxysmal psychological disorders, which in four cases were certainly of an epileptic nature, showed seizure patterns in their electroencephalograms at megimide concentrations varying from 0·3 to 1·8 milligrammes per kilogram (mean, 1·0 milligramme per kilogram). Our control figures for non-epileptics showed that megimide did not produce seizure patterns in the electroencephalogram at concentrations varying from 2·0 to 2·7 milligrammes per kilogram, and, according to French workers, the critical megimide concentration was considerably higher. A comparison between the figures of the critical megimide concentration of epileptics (mean, 1·0 milligramme per kilogram) with that of non-epileptics (more than 2·0 milligramme per kilogram) suggests that the use of megimide activation in electroencephalography for the diagnosis of epilepsy is a valid method. However, megimide is able to induce all the different known forms of seizure patterns in the electroencephalogram, the slow-wave seizure patterns tending to require, as a rule, more megimide than the other forms of seizure patterns.

A short note about the reliability of megimide activation in the electroencephalogram has to be added. One patient (Case 6) had no seizure patterns after the administration of 14 cubic centimetres of the megimide solution. The same patient, on another occasion, when he received three milligrammes of "Serpasil", showed seizure patterns in the electroencephalogram after the injection of only six cubic centimetres of megimide solution. The different results could be explained by the unknown additional effect of "Serpasil", but could also well be an expression of spontaneous variations of the epileptic threshold in epileptics.

Clinical Epileptic Seizures Produced by Megimide.

The French workers did not hesitate to administer megimide continuously until the drug precipitated the specific critical form of convulsive crisis which, they state, occurred before a generalized major seizure took place.

We were reluctant to risk major seizures, but accidentally produced a convulsive crisis in nine patients. Five patients exhibited myoclonic seizures, one had an olfactory seizure, one had a "queer sensation in the stomach", and two had major seizures.

We had the distinct impression that the margin between the quantity of megimide that resulted in seizure patterns in the electroencephalogram and the quantity that produced a major generalized seizure was quite appreciable. Megimide in four cases (Cases 13, 20, 22 and 28), even in the absence of photic stimulation, caused so many rhythmically recurring seizure patterns that we expected a major seizure, which, however, did not occur. According to our experiences, "Metrazol" would have precipitated a major seizure in these cases. That a major seizure in two of our cases did occur with megimide we think was due to the too-rapid initial injection of the drug. Subsequent to this series of 30 patients in whom we injected megimide, we changed our injection technique. From the beginning we injected only two cubic centimetres of the megimide solution at a time within about sixty seconds, instead of six cubic centimetres within fifteen seconds, as suggested by the French workers. We were, by this means, able to avoid any "spurious" seizure patterns and generalized major seizures.

Side-Effects of Megimide.

In none of our 30 cases could any symptoms or signs directly attributable to the megimide be observed. Of course, this does not apply to the megimide-induced convulsive crises. Megimide, in this respect, contrasts favourably with "Metrazol", which often produces intense nausea and fear.

"Sodium Pentothal" and Megimide.

Megimide was originally used to counteract barbiturate narcosis. We tested inversely the effect of a barbiturate, "Sodium Pentothal", given intravenously, on megimide-produced seizure patterns.

Peacock (1956) and Cass (1956) describe the electroencephalographic changes that occur during the administration of megimide in barbiturate anæsthesia. Inversely, we found in four cases that the electroencephalographic seizure patterns usually ceased sixty to eighty seconds after the injection of "Sodium Pentothal". On one occasion we also observed bursts of high-voltage slow waves in both frontal regions, the significance of which is not clear to us.

In comparing the megimide-"Pentothal" effect with the "Metrazol"-"Pentothal" effect on the electroencephalogram, we had only one "Metrazol" case at our disposal (Case 2), in which we terminated the theta-wave seizure patterns with "Sodium Pentothal"; this happened eighty seconds after the injection. In this single case, therefore, "Sodium Pentothal" neutralized the epileptogenic effect of "Metrazol" as promptly as it did that of megimide.

Activating Effect of Megimide, "Metrazol" and Natural Sleep.

One patient (Case 2) did not show any seizure patterns or larval seizure patterns at a megimide concentration of 1·8 milligrammes per kilogram, while "Metrazol", at a body concentration of six milligrammes per kilogram, and natural sleep also, produced theta-wave seizure patterns. However, this case is not much use for the purpose of comparing the effect of the two drugs, as a higher body concentration of megimide may still have produced the specific seizure patterns obtained by other means. This test only shows that, in a certain patient, more than 1·8 milligrammes per kilogram of megimide may have an identical electroencephalographic effect to six milligrammes per kilogram of "Metrazol".

Prefrontal and Frontal Theta-Waves Produced by Megimide.

Megimide produced prefrontal and frontal theta-waves of an amplitude of 30 to 60 microvolts in many of our patients, epileptics and non-epileptics alike. We observed this phenomenon clearly in six out of the 30 patients. The concentration of megimide in the body necessary to produce these theta-waves varied from 1·0 to 2·7 milligrammes per kilogram. Less dramatically, though still significantly, megimide increased already existing frontal theta activity in 16 of the remaining 24 patients. In these cases the megimide body concentration varied from 0·6 to 1·7 milligrammes per kilogram (mean, 1·1 milligrammes per kilogram). Megimide did not produce any theta-waves in the electroencephalograms of the remaining eight patients, who received the drug at concentrations varying from 0·3 to 1·3 milligrammes per kilogram (mean, 0·9 milligramme per kilogram). These figures suggest that the production of the prefrontal and frontal theta-waves depends on a high concentration of megimide in the body.

Drossopoulo *et alii* (1956) mention that megimide, in normal and abnormal subjects, produces in the electroencephalogram "progressive modifications in the form of slow bilateral synchronous activity". We assume that this "slow bilateral synchronous activity" is identical with the prefrontal and frontal theta-waves we have observed, although we did not always notice synchrony in both hemispheres. They further mention that the same slow activity is also produced by "Metrazol". Going through our old "Metrazol" electroencephalographic recordings, we found inded a few tracings showing some frontal theta-activity. The "Metrazol"-produced theta-waves were, however, considerably less marked and often absent compared with the megimide-produced theta-waves. Our impression is that megimide produces more theta-activity than "Metrazol".

We began to speculate about the significance of megimide-produced prefrontal and frontal theta-waves. In routine electroencephalograph work theta-waves may be correlated with emotional immaturity, but this theta-rhythm was not present in the resting record. Pathological lesions in the diencephalon produce the theta-abnormality, and it is possible that stimulation in this area is a result of the administration of the megimide. It is also possible that the theta-waves appear as a result of the exhaustion of cortical nerve cells. The latter hypothesis is supported by the observation of theta and delta activity (presumably due to syphilitic cortical lesions) in the prefrontal and frontal electroencephalogram of one patient (Case 3), who suffered from general paralysis of the insane; this theta and delta activity increased considerably in amplitude after the injection of megimide. Metabolic exhaustion of the frontal cortical neurons and to some extent of the diencephalic structures connected to the frontal lobes seems to be a possible explanation of the appearance of prefrontal and frontal theta-waves under the effect of megimide.

It was decided to investigate specifically the possibility that the theta-waves were an early expression of the convulsive tendency produced by megimide. This explanation was suggested by our observation that epileptics often had frontal theta-waves which disappeared (giving place to small spikes) after the administration of anticonvulsive drugs. However, the findings did not support such an explanation. Only two out of six patients with megimide-induced theta-waves had electroencephalographic seizure patterns, while 21 out of 24 patients with few or no megimide-produced theta-waves showed seizure patterns in their electroencephalograms. These results in fact suggested that, contrary to our suspicion, the prefrontal and frontal theta-waves seemed to exert an unfavourable influence for the development of seizure patterns. However, the inference has to be accepted with caution, as the irregular distribution of seizure patterns among the theta-wave and non-theta-wave patients may be the result of chance. Furthermore, the patients who exhibited theta-waves had received larger amounts of megimide and were therefore more likely to be non-epileptics than the patients without theta-waves, who had received a smaller quantity of megimide sufficient to show up seizure patterns in epileptics. Nevertheless the hypothesis that megimide-produced theta-waves have an inhibiting effect on the convulsive process is a tempting postulation, since, according to Gastaut (1954), theta-waves and delta-waves have an inhibiting effect on electroencephalographic spikes, which initiate the major seizures; this may explain the suspected greater margin of safety of megimide in comparison with "Metrazol", which produces less theta-activity.

Megimide Activation of Slow Waves in Cerebral Lesions.

In one patient (Case 14), with a temporal epileptogenic focus, megimide produced continuous high-voltage slow activity in the same area. In the case of the patient (Case 3) suffering from a syphilitic inflammation of the cortex of the frontal lobe, megimide increased the voltage of the slow-wave activity. These two observations suggest that it may possibly be profitable to use megimide to show up small cerebral lesions in the electroencephalogram which are not evident in routine electroencephalograms. However, further investigations have to be made to substantiate this suggestion.

Localization of Megimide Activity.

The seizure patterns most frequently brought out by megimide were of the myoclonic, poly-spike-wave and spike-and-wave forms. According to Jasper (1954), these types of seizure pattern usually originate in, or involve mainly, cellular structures around the third ventricle or the upper

part of the brain-stem. Megimide seems, therefore, to have a stimulating effect on these structures.

The megimide-produced prefrontal and frontal theta-waves, as already mentioned, may be due to changes of the metabolism of neurons in the cortex. This hypothesis is supported by the already mentioned observation in the patient (Case 14) with a temporal epileptogenic focus, in whom megimide produced high-voltage slow waves in the same area.

Summary.

1. Megimide given intravenously and photic stimulation were used as convulsive activators for the electroencephalographic diagnosis of epilepsy in 30 patients, of whom eight were suffering habitually from major seizures, eight from undiagnosed physical "fits", 12 from paroxysmal psychological disorders, and one from general paralysis of the insane; one was a non-epileptic several years after insulin-coma treatment.

2. All the eight epileptics and 10 out of the 12 patients suffering from paroxysmal psychological disorders showed seizure patterns or larval seizure patterns in the electroencephalogram at significantly smaller megimide concentrations in the body than those of the remaining group of patients. All the known characteristic forms of seizure patterns were encountered. An epileptogenic temporal focus in one patient was activated by megimide.

Four of seven patients suffering from paroxysmal behaviour disorders, in whom megimide produced seizure patterns in the electroencephalogram, improved clinically with anticonvulsive treatment. These observations made us conclude that megimide could be used as a specific and valuable activator for the electroencephalographic diagnosis of epilepsy, as had been claimed by various French workers.

3. Megimide has several advantages in comparison with "Metrazol"; it has no side-effects, and probably a greater margin of safety than "Metrazol".

4. Clinical convulsive crises were unwittingly produced with megimide in several patients. In at least one patient the convulsive crisis corresponded to the clinical complaint. This supports the claim of the French workers, who are using megimide for the production of clinical convulsive crises for diagnostic purposes.

5. "Sodium Pentothal" given intravenously stops megimide-produced electroencephalographic seizure patterns within sixty to eighty seconds, and can therefore be used to stop impending megimide-produced major seizures.

6. Megimide produced prefrontal and frontal theta-waves, which seem to have a slightly inhibiting effect on the convulsive process.

7. The hypothetical action of megimide on the cortex and on diencephalic structures is discussed.

8. Further investigations of the use of megimide in activating the electroencephalogram of cerebral (non-epileptic) lesions are suggested.

9. The initial injection of six cubic centimetres of the megimide solution suggested by French workers seems to be too rapid, as it may cause "spurious" seizure patterns in the electroencephalogram and actually precipitate clinical major seizures.

Acknowledgements.

I wish to thank Professor F. H. Shaw for having suggested the investigation of megimide, and for arranging for the supplies of megimide solution and of the literature about the effects of megimide. My thanks also go to the Mental Hygiene Authority of Victoria for allowing us to test the drug and for giving us permission to publish the article; to Dr. A. Stoller, Chief Clinical Officer, who provided us with both help and advice in the production of this paper; and finally to Sister J. L. Dean and Mr. H. B. Bratspies, F.R.T.C., electrophysicist, for their loyal work in our Electroencephalographic Department at Mont Park.

References.

CASS, N. M. (1956), "An Electroencephalographic Study of the Analeptic Action of β-ethyl β-methyl glutaramide (Megimide)", *Brit. J. Anæsth.*, 28: 325-336.

DELAY, J., VERDEAUX, E., DROSSOPOULO, G., SCHULLER, E., and CHANOIT, P. (1956), "*Un neuro-stimulant épileptogène. La mégimide*", *Presse méd.*, 64: 1525.

DELAY, J., SCHULLER, E., DROSSOPOULO, G., HAIM, A., CHANOIT, P., and VERDEAUX, J. (1956), "A New Activating Agent of the Electroencephalogram (N.P. 13, Megimide)", paper presented to the *Société de biologie*, February 11, 1956.

DROSSOPOULO, G., GASTAUT, H., VERDEAUX, J., and SCHULLER, E. (1954), "Comparison of E.E.G. 'Activation' by Pentamethylenetetrazol (Metrazol) and Bemegride (Megimide)", *Faculté de Médecine*, Marseilles (personal communication).

GASTAUT, H. (1954), "The Epilepsies", Thomas, Springfield: 66.

PEACOCK, J. M. (1956), "An Electroencephalographic Examination of the Effects of Megimide and Daptazole in Barbiturate Narcosis", *Electroencephalog. & Clin. Neurophysiol.*, 8: 289.

PENFIELD, W., and JASPER, H. (1954), "Epilepsy and Functional Anatomy", Churchill, London: 622.

SHAW, F. H., SIMON, F. E., CASS, N., SHULMAN, A., ANSTEE, G. L., and NELSON, E. B. (1954), "Barbiturate Antagonism-D", *Nature*, 74: 402.

Reports of Cases.

THE USE OF CHLORPROMAZINE TO CONTROL SPASM AND RIGIDITY IN TETANUS: REPORT OF A CASE.

By F. I. R. MARTIN.[1]

From the Clinical Research Unit of the Royal Melbourne Hospital and the Walter and Eliza Hall Institute of Medical Research, Melbourne.

As tetanus is a disease which is seen only rarely in any one centre, new methods of treatment may take some time to be evaluated and generally accepted, so that the preliminary report of the successful use of a drug is wise. Further, the therapy in current favour, despite the use of heavy sedation, muscle relaxants and even artificial respiration and tracheotomy, is not satisfactory in every case. It often has the disadvantage of being complicated and requiring specialized nursing and medical care, which makes the application in small hospitals very difficult.

It is of importance that the mortality from tetanus, which could be a preventible disease with immunization as shown in the second World War (Boyd, 1946; Cutler, 1947), is still high. A review of cases of tetanus treated in this hospital in the ten years up to 1955 gives a mortality rate of 30%, and other Australian writers give figures from 31% to 47% (Johnson, 1956). In this hospital, since the great reduction in the gross mortality from tetanus with the advent of penicillin, there has been no further significant reduction in mortality from this disease. This is despite the use of new methods of treatment over the last five years (Saint *et alii*, 1953; Last and Nicholas, 1956). This fact was also noted by Johnson in his review of Queensland cases.

For these reasons, any new form of therapy which may offer some advance is worth recording.

There have been recent reports of the use of chlorpromazine in tetanus (Cole and Robertson, 1955; Kelly and Laurence, 1956) and other spastic states (Basmajion and Szatmari, 1955). These have been favourable, and they suggested its use in the case recorded here.

Clinical Record.

A man, aged twenty-six years, was admitted to the Clinical Research Unit of the Royal Melbourne Hospital sixteen days after he had been accidentally shot at short range in the right thigh with a blank cartridge from a shotgun. At the time of injury, *débridement* and partial closure of the wound had been performed, and it was stated that tetanus antiserum was given. Later, the

[1] Drug Houses of Australia Fellow.

wound discharged pus and wads of cartridge, but was not painful. Two days before his admission to hospital he noticed difficulty in opening his mouth to eat. This became more pronounced in the next twenty-four hours, and was associated with stiffness of the right leg.

When the patient was first seen in this unit, there were slight *risus sardonicus* and trismsus, and the tone of his abdominal muscle was increased, but it was not rigid. The right leg was stiff, and the deep reflexes were greatly increased. There had been no generalized spasms, and he had no respiratory or pharyngeal distress. A diagnosis was made of tetanus of moderate severity only, and treatment with large doses of tetanus antiserum and penicillin was commenced. It was decided to try to control the rigidity with continuous heavy sedation, a barbiturate being used. The wound was widely excised on the evening of his admission to hospital, and slight anæmia was corrected by blood transfusion. His hæmoglobin value was subsequently maintained. Examination of a blood film on his admission to hospital revealed gross neutrophilia (24,000 per cubic millimetre). Because of recent experience with bone-marrow depression in severe tetanus (Lassen *et alii*, 1956; Wilson *et alii*, 1956), a sternal puncture marrow biopsy was undertaken; this revealed normal erythropoiesis, and throughout the course of his illness there was no evidence of thrombocytopenia or agranulocytosis on repeated blood examination.

Five days after his admission to hospital, the rigidity had become more pronounced, the abdomen was board-like and slight opisthotonos was present. An indwelling catheter was inserted because of retention of urine. The sedation was increased; but with any painful or noisy stimulus the patient developed painful spasms, mainly of the right leg, but with some general radiation. It was obvious that the condition was not so mild as had at first been hoped.

On the ninth hospital day the rigidity and superimposed spasms were severe and painful. Mephenesin ("Myanesin") was given by mouth; but after he had received a total of three grammes of mephenesin in twelve hours, hæmoglobinuria developed, with the passage of many red cells and casts in the urine. The urine cleared in twenty-four hours after administration of the drug was stopped.

As a result of discussion with Dr. Patricia Wilson, of the Department of Anæsthesia, Royal Melbourne Hospital, chlorpromazine therapy was commenced; 20 milligrammes (diluted to 10 cubic centimetres with sterile water) were injected intravenously. Two minutes after the injection there was complete relaxation of the abdominal muscles and the limbs, the tone of the muscles in the back was normal, and the patient could open his mouth one inch instead of half an inch as before. Ten minutes later the patient was asleep and fully relaxed. The blood pressure fell only slightly—from 120 to 100 millimetres of mercury, systolic, and from 80 to 70, diastolic—measured with the patient lying down. For the first two hours after the injection relaxation was excellent, and for the next four hours the patient remained comfortable, with only moderate rigidity, but no spasms. The same effect was produced each time the drug was given; but doses were increased up to 40 milligrammes to give longer action with no more hypotensive effect. These were usually necessary every six to eight hours. Chlorpromazine (50 milligrammes) was also given intramuscularly, but did not produce such satisfactory relaxation, and the duration of action was variable.

Treatment with intermittent intravenous injections of chlorpromazine during the day, and oral barbiturate sedation with intramuscular chlorpromazine injections at night, was continued for seven days. The patient was comfortable, nursing care and physiotherapy could be given without causing painful spasms, and his general condition improved. He was then maintained on intramuscular chlorpromazine therapy (50 milligrammes thrice daily) for a further three days before the drug was discontinued. No toxic effects were observed with the drug.

After removal of the self-retaining catheter, there was a brief period of pyrexia associated with a urinary infection, which rapidly responded to tetracycline. The chest remained clinically and radiologically normal. A skin grafting operation was performed on the wound in the thigh sixteen days after excision, and the patient was discharged from hospital five weeks after his admission.

The duration of the rigidity and spasm was twenty-one days, and this was controlled by chlorpromazine for the last ten days. Divided doses of the order of 100 to 120 milligrammes per day given intravenously, and 50 milligrammes per day given intramuscularly, were used.

Comment.

A case of tetanus of moderate severity, in which rigidity and spasm were controlled with chlorpromazine, is presented. It is probable that in this particular case other standard methods of treatment could have adequately controlled the condition. However, chlorpromazine proved very satisfactory in producing both adequate relaxation and sedation, without requiring either deep anæsthesia or the need for artificial respiration.

Previous reports of the use of chlorpromazine in tetanus have been few. Kelly and Laurence (1956) used it with good effect in experimental tetanus in rabbits. Later, in a case of severe tetanus in a child, aged two and a half years, they used a continuous intravenous infusion with intermittent injections of chlorpromazine into the drip apparatus, with an excellent result. Their dosage was relatively much higher than that used here, and followed an initial test dose of 15 milligrammes well diluted. Working in East Africa, Cole and Robertson (1955) reported six cases of tetanus in which chlorpromazine was used in addition to sedation with phenobarbital and chloral hydrate, with good effect. They stressed the simplicity of this treatment, and the added advantage of the "euphoric effect" of the drug. A similar action of chlorpromazine in reducing the rigidity and spasm associated with severe Parkinson's disease is described by Basmajion and Szatmari (1955); these writers also advocated its trial in tetanus.

Toxic effects reported are of extensive intravenous thrombosis following the continuous infusion method of Kelly and Laurence. However, the general complications of chlorpromazine therapy should be remembered, notably jaundice, agranulocytosis and skin sensitivity. The individual response, particularly to chlorpromazine given intravenously, is very variable, and a trial dose of 15 to 20 milligrammes, well diluted and given slowly, should be used first.

Although Burn (1954) reported a direct relaxant effect on isolated muscle in animal experiments, it is generally believed that the action of chlorpromazine is central (Goodman and Gilman, 1955; Dobkin *et alii*, 1954). Kelly and Laurence suggest that in addition there may be a local action in the spinal cord, the internuncial neurons which relay the spinal reflexes being depressed.

It is unlikely that chlorpromazine will prove effective in all cases of severe tetanus; but the evidence so far indicates that it has a definite place in treatment. The administration is relatively simple and safe; also it can be used in association with other already recognized methods of treatment. Probably it will be of most use in cases of moderate severity, as described here, and in severe cases in the stage of recovery.

It is hoped that reports of experiences with chlorpromazine in cases of tetanus in other centres will follow.

Summary.

1. A case of tetanus of moderate severity is described, in which chlorpromazine given parenterally allayed spasms and produced good muscular relaxation and sedation.

2. The relaxant effect was immediate and prolonged, six-hourly to eight-hourly intravenous injections being required.

3. The literature on this use of chlorpromazine is briefly reviewed, and further trials of the drug, either alone or in association with other sedatives, are advocated in tetanus.

Acknowledgements.

I wish to thank Dr. Patricia Wilson, of the Department of Anæsthesia, Royal Melbourne Hospital, for advice in the treatment of this patient, and Dr. Ian Wood, Head of the Clinical Research Unit, for permission to publish the report of this case.

References.

BASMAJION, J. V., and SZATMARI, A. (1955), "Effect of Largactil (Chlorpromazine) on Human Spasticity and Electromyogram: A Preliminary Report", *Arch. Neurol. & Psychiat.*, 73: 224.

BOYD, J. S. K. (1946), "Tetanus in the African and European Theatres of the War", *Lancet*, 1: 113.

BURN, J. H. (1954), "Pharmacology of Chlorpromazine and Promethazine", *Proc. Roy. Soc.*, 47: 617.

COLE, A. C. E., and ROBERTSON, D. H. H. (1955), "Chlorpromazine in the Management of Tetanus", *Lancet*, 2: 1063.

CUTLER, E. C. (1947), "Experiences of Army Doctor in European Theater of War", *Am. J. Surg.*, 73: 637.

DOBKIN, A. B., GILBRETH, R. G. B., and LAMOUREUX, L. (1954), "Physiological Effects of Chlorpromazine", *Anæsthesia*, 9: 157.

GOODMAN, L. S., and GILMAN, A. (1955), "The Pharmacological Basis of Therapeutics", Macmillan, New York: 1066.

JOHNSON, D. W. (1956), "Epidemiology of Tetanus in Queensland", M. J. AUSTRALIA, 2: 710.

KELLY, R. E., and LAURENCE, D. R. (1956), "Effect of Chlorpromazine on Convulsions of Experimental and Clinical Tetanus", *Lancet*, 1: 118.

LASSEN, H. C. A., HENRIKSEN, E., NEUKIRCH, F., and KRISTENSEN, H. S. (1956), "Treatment of Tetanus: Severe Bone Marrow Depression after Prolonged Nitrous-Oxide Anæsthesia", *Lancet*, 1: 527.

LAST, P. M., and NICHOLAS, J. (1956), "The Treatment of Tetanus by Sedation, Curarization and Intratracheal Positive-Pressure Artificial Respiration, with Report of a Case", M. J. AUSTRALIA, 2: 374.

SAINT, E. G., JOSKE, R. A., and STUBBS, J. L. (1953), "The Treatment of Tetanus", M. J. AUSTRALIA, 1: 361.

WILSON, P., MARTIN, F. I. R., and LAST, P. M. (1956), "Bone Marrow Depression in Tetanus: Report of a Fatal Case", *Lancet*, 2: 442.

Reviews.

Roentgen Changes in the Cranium in 153 Intracranial Tumours in Children Aged 0-15 Years. By Helge Hertz, M.D., and Thomas Rosendal, M.D.; 1956. Stockholm: Acta Radiologica (Supplement 141). 9¾" × 7", pp. 56, with 32 illustrations. Price: Sw. Kr. 30.

THIS book deals with intracranial tumours in children, which have not received much attention hitherto. All previous communications have dealt with tumours in the adult. In children the tumours are generally gliomata, and are mostly confined to the posterior fossa. Craniostasis is common in children, and the skull may increase considerably in size. Suture diastasis is calculated by measurement of the coronal suture. In the cases reported the diagnosis has been confirmed by operation or autopsy. Of the tumours, 75% were gliomata (Cushing 77%). The examinations were made in the frontal, right and left lateral and Towne's positions. These views allowed of correct diagnosis in 80% of cases, and in 30% calcification or changes were found in the cranial walls. Displacement of the pineal body was of help in some instances. Various methods of measurement of the cranial capacity are described. The illustrations are of excellent quality and most interesting. The monograph is a monument to the painstaking efforts of the authors, and is well worthy of study.

The Year Book of the Eye, Ear, Nose and Throat (1956-1957 Year Book Series). "The Eye", edited by Derrick Vail, B.A., M.D., D.Oph. (Oxon.), F.A.C.S., F.R.C.S. (Hon.); "The Ear, Nose and Throat", edited by John R. Lindsay, M.D.; 1957. Chicago: The Year Book Publishers, Incorporated. 7¾" × 5¼", pp. 448, with 128 illustrations. Price: $7.00.

THERE has been no change in the editorship of the 1956-1957 "Year Book of the Eye, Ear, Nose and Throat"; the section on the eye is edited by Derrick Vail, and that on the ear, nose and throat by John R. Lindsay. The titles of the subsections in the parts of the book dealing with the eye and ear have also not been changed. In the sections on the nose and throat some telescoping has been carried out, so that there are now subsections on the larynx and neck, the trachea, bronchi and tracheotomy, and the hypopharynx and œsophagus, and a new subject, acute respiratory disease viruses, has been introduced. The editors have followed their usual custom of making comments on the papers abstracted whenever these appear to them to be necessary. This Year Book provides, as before, a valuable source of up-to-date information in the particular specialties it covers.

Developmental Abnormalities of the Eye. By Ida Mann, C.B.E., M.A. (Oxon.), D.Sc., M.B., B.S. (Lond.), F.R.C.S. (Eng.), F.R.A.C.S.; Second Edition; 1957. London: British Medical Association. 9¾" × 6", pp. 432, with 284 illustrations. Price: 90s.

SINCE the publication in 1937 of the first edition of Professor Ida Mann's monograph "Developmental Abnormalities of the Eye", "one or two outstanding advances in knowledge have been made", which have had a profound influence on our understanding of the developmental pathology of the eye. The relationship between maternal rubella and certain types of congenital cataract, to which Gregg drew attention, has provided an example of the "noxious agent" acting transplacentally to help to prove the thesis which Professor Mann elaborated in the first chapter of the original edition.

Terry's description of the new disease of retrolental fibroplasia led to a world-wide investigation of this condition, which was causing much blindness amongst premature infants, a greater percentage of whom survived owing to the improved modern methods of post-natal care. Terry's early death robbed him of the opportunity of anticipating the observation of Kate Campbell, a Melbourne pædiatrician, that excessive oxygen therapy was the causative factor.

It must be admitted that, at the time of the first publication of Professor Mann's monograph, the study of the developmental abnormalities of the eye appeared to be purely of academic interest and of no practical value. Research on these two diseases has shown, in startling fashion, that some at least of the developmental anomalies of the body can be prevented, and has opened up new vistas in the approach to them.

Professor Mann's book still remains unique in the English literature of ophthalmology, and one of the most fascinating. The possessors of the first edition will find the purchase of the second one well worth while because of its additional subject matter. One cannot agree too heartily with the American reviewer of twenty years ago that it is a classic.

Physiopathology of the Reticulo-Endothelial System: A Symposium Organized by the Council for International Organizations of Medical Sciences Established under the Joint Auspices of UNESCO and W.H.O. Edited under the direction of B. N. Halpern by B. Benacerraf and J. F. Delafresnaye, C.I.O.M.S.; 1957. Oxford: Blackwell Scientific Publications. 8½" × 5½", pp. 330, with many illustrations. Price: 45s.

THIS monograph records the proceedings of a symposium in which the participants were distinguished investigators from France, Switzerland, Germany, the United States of America and Great Britain. In addition to the formal papers there is a summary of the discussions arising therefrom. The object of the symposium was to discuss certain aspects of the reticulo-endothelial system—*viz.*, phagocytosis, metabolic functions and the role of the system in defence against bacterial infection. Each paper is concerned with the experimental approach, and only rarely is human pathology mentioned. Naturally there is a good deal of overlapping, but in general the papers deal with distinct facets of the subject. Several papers deal with the mechanism of phagocytosis and the modifying effects of corticoids, irradiation and non-specific blockade. It was interesting to learn that many experiments in which the phagocytes have been blockaded by carbon particles are invalid by reason of the toxicity of the shellac in commercial indian ink used for the purpose.

Methods of stimulating the reticulo-endothelial system are discussed. One which may have some value in human therapeutics is the use of colloidal aggregates of heterologous albumin and globulin.

Immunological problems, such as antibody formation, sensitivity reactions and the detoxification of certain bacterial products, are the subjects in other papers.

Two papers are devoted to the function of the reticulo-endothelial system in eliminating worn-out blood cells from the circulation. They also discuss the nature of hyper-

splenism. Other papers dealt with such diverse subjects as the anatomy and physiology of the reticulo-endothelial system, the shape of macromolecular substances in solution, iron metabolism, the clearing of lipids from plasma and the causation of ascites in experimental cirrhosis.

Substantial advances have been made in our knowledge of the functions of the reticulo-endothelial system, and some of its more mysterious reactions such as the Schwartzmann reaction are beginning to be comprehensible. Anyone wishing to keep informed of the trends of research in this system will enjoy this book. It should be useful also to those engaged in teaching, for they will find much to supplement the ordinary sources of information.

Antibiotics Annual, 1956-1957: Proceedings of the Fourth Annual Symposium on Antibiotics: Sponsored by U.S. Department of Health, Education, and Welfare, Food and Drug Administration, Division of Antibiotics; in Collaboration with the Journals Antibiotics and Chemotherapy, and Antibiotic Medicine and Clinical Therapy. Edited by Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.; 1957. New York: Medical Encyclopedia, Inc. 10" × 6¾", pp. 1152, with many figures. Price: $10.00.

THIS, the latest volume of the "Antibiotics Annual", contains the proceedings of the fourth Annual Symposium on Antibiotics held at Washington, D.C., in October, 1956. The chairman of the symposium was Henry Welch, director of the Division of Antibiotics, Food and Drug Administration in the United States Department of Health, Education and Welfare, which sponsored the symposium. The volume contains 155 individual papers as well as the reports of three panel discussions. The papers record investigations into the use of a wide variety of antibiotics, particularly those more recently introduced, and five new antibiotics are described. The panel discussions deal with antibiotics in intestinal antisepsis, the susceptibility of microorganisms to antibiotics isolated from hospitalized and non-hospitalized persons and the present status of antibiotics in the preservation of food. These general subjects also figure largely in the individual papers. A great deal of the material in this volume will be of interest only to those with a specialist interest in antibiotics and their development, but the general clinician will at least wish to browse through it. In an interesting introductory paper on antibiotics and the problem of medical communication, Félix Martí-Ibáñez discusses the general questions of developments in antibiotic knowledge and their communication to the world, and advocates the establishment of chairs in antibiotic medicine in various countries of the world as well as an international institute of antibiotics dedicated exclusively to organizing knowledge in this field.

Schizophrenia, 1677: A Psychiatric Study of an Illustrated Autobiographical Record of Demoniacal Possession. By Ida Macalpine, M.D., and Richard A. Hunter, M.D., M.R.C.P., D.P.M.; 1956. London: William Dawson and Sons, Limited. 9¾" × 7¼", pp. 208, with 13 illustrations. Price: £6 10s.

THE core of this book is a re-presentation of a manuscript relating the story of the illness of Christoph Haitzmann. This history was the subject of an analysis by Freud under the title "A Neurosis of Demoniacal Possession in the 17th Century". It is said that upon this case and the better known Schreber memoirs, Freud first formulated his theory that "paranoia" could be explained on the basis of a conflict over unconscious homosexuality. Freud's views on this matter, which have been the subject of controversy ever since, are discussed in detail and largely refuted in this book. The authors' thesis is, in short, that in both Haitzmann's and Schreber's cases, the underlying psychological mechanism was not that of a conflict over homosexual feelings, but "confusion and uncertainty as to sexual identity accompanied by the emergence of archaic procreation fantasies".

While it is stated that Freud made interpretations in his analysis of this case which were hardly justified by the amount of material available, the reader may be of the opinion that Macalpine and Hunter have tended in the same direction. Although stories of demoniacal possession undoubtedly provide fascinating material for conjecture, this account, in common with others, does not appear sufficiently well documentated to allow of very valid reappraisal with the passage of years, even when the original material is re-examined. Despite this, and despite the somewhat tendentious analysis which forms the major part of the work, there is much here which is of interest to students of psychopathology.

One unusual feature of the book is the inclusion of a series of coloured reproductions of Haitzmann's paintings of the devil, who, it is said, appeared to him on a number of occasions. Although his illness may well have interfered with the painter's technical ability, it is perhaps fair comment to suggest that there is nothing in these pictures to indicate that he was an artist of any great merit.

The Year Book of Orthopedics and Traumatic Surgery (1956-1957 Year Book Series). Edited by Edward L. Compere, M.D., F.A.C.S., F.I.C.S.; 1957. Chicago: The Year Book Publishers. 7¾" × 5", pp. 336, with 208 illustrations. Price: $6.75.

As in previous years, "The Year Book of Orthopedics and Traumatic Surgery" is edited by Edward L. Compere. The titles of sections set out in the table of contents are unchanged except for two additions—sprains are considered in the section on fractures and dislocations, and there is a new section on "geriatric orthopedics". In his introduction, the editor refers to the growing interest in the diseases or disabilities of the older patient, and states that this is making geriatrics a subject which must be studied by every orthopædic surgeon who wishes to be well informed. The editor also makes some pertinent remarks about the causes of non-union or delayed union in fractures of the spine and extremities, about the value of small bone grafts when open operation cannot be avoided in the treatment of non-union or delayed union in such fractures, and on the uses and abuses of antibiotics in the light of recent discussions. This Year Book will be as useful in its own field as all those which have preceded it.

A Radiologic Study of the Brain Circulation by Rapid Serial Angiography of the Carotid Artery. By Torgny Greitz; 1956. Stockholm: Acta Radiologica (Supplement 140). 9¾" × 7", pp. 124, with 28 illustrations. Price: Sw. Kr. 30.

THIS monograph is an account of investigations by the author into some fundamental points in cerebral angiography. The nature of the problems considered and the descriptive terms used are clearly defined at the outset. The following problems were investigated: (i) the effect of the angiographic procedure on the circulation; (ii) the use of rapid serial angiography in measuring circulation times, and the value of rapid serial angiography in neuroradiological diagnosis.

Four chapters are devoted to the first problem, and it is in these that the most valuable part of the work is described. Three chapters are then given to a description of findings demonstrated by rapid serial angiography in various diseases. The book ends with a general summary and a bibliography.

This work is of interest to the neurosurgeon and radiologist, in that it records a valuable basic research on time factors in cerebral angiography.

Notes on Books.

The Diabetic Journal of Australia. Published quarterly by the Diabetes Federation of Australia, 107 Bathurst Street, Sydney, in the interests of diabetics and the public generally. Price: 1s. 3d.

THE Diabetes Federation of Australia is a registered charity, which came into being in 1956 as the result of a decision of the Diabetic Associations of Victoria, South Australia, Tasmania and New South Wales. The objects of the Federation are "to help the diabetic patient to understand his complaint and to adjust himself to the necessary routine, and to consider his welfare in every way possible to a lay organization" (M. J. AUSTRALIA, October 6, 1956, page 533). One of the activities of the Federation is the production of a quarterly journal for diabetics, the first number of which appeared in January, 1957. This issue contains several messages of goodwill from overseas; three have been sent respectively by Dr. R. D. Lawrence (President of the International Diabetes Federation), Dr. Elliott P. Joslin (Honorary President of the International Diabetes Federation) and Dr. Charles H. Best (Honorary President of the International Diabetes Federation). As well as setting out the history and constitution of the Diabetes Federation of Australia, the January issue of the journal provides information on such subjects as life insurance for diabetics, the new antidiabetic substances for oral administration, suggested medical standards for diabetic children's camps, meals out

of doors, and diabetic clinics in the several States. From a perusal of this and subsequent issues, it is obvious that the journal should be of real help to diabetics. It is well produced, easy and pleasant to read, factual and attractive.

Sydney Looks Back. By Isadore Brodsky; 1957. Sydney, London, Melbourne, Wellington: Angus and Robertson. 8¾" × 5¼", pp. 256, with many illustrations. Price: 42s.

THE author of this book, a medical practitioner, lived as a child two hundred yards from the Sydney General Post Office, which in those days had a chiming clock, and Sydney is to him as London is to one born within the sound of the Bow Bells. In this volume he has gathered together a wealth of facts, anecdotes and reflections relating to old Sydney—not just the Sydney of his youth, but also the rambling town of the early days as it grew around Sydney Cove and the Tank Stream in the haphazard way that still perversely accounts for much of its charm. "Sydney Looks Back" is made up of a series of short articles, each complete in itself and dealing with some facet of the city; some idea of its scope will be seen from the headings under which these articles are grouped: "Places", "Theatre", "Persons", "Pastimes", "Civic", "Sport", "Commerce", "Transport". Dr. Brodsky's style is unpretentious and well matched to the quiet and affectionate way in which he approaches his material. We can feel that we are looking over his shoulder as he thumbs through old newspapers, or strolling through the streets of old Sydney amongst the ordinary people on any day or night of the week. Printed and bound by the Halstead Press, in a fashion of which they may well be proud, this book should appeal to all who know and love Sydney. Those who do not really know her, especially those from her more ordered sister capitals, may well find in this book the key to her wayward charm.

New Appliances.

THE McRAE RUSSELL MICROSCOPE STAGE.[1]

WHEREAS the usual microscope mechanical stage for the direction of slides is an expensive piece of apparatus, moving by geared action in two directions, the stage here described

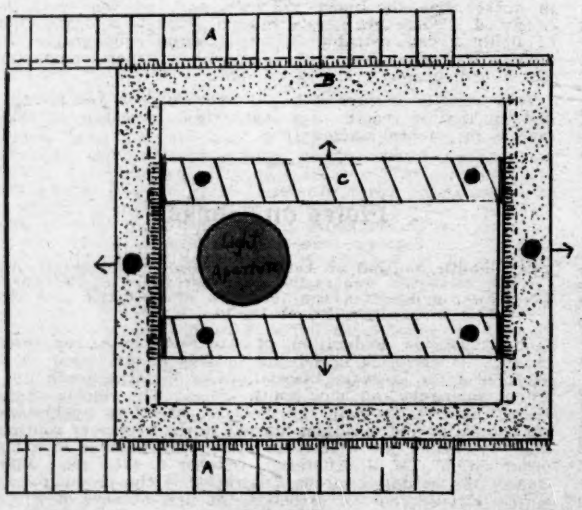

FIGURE I.

A and A1, guide members; B, guide frame; C, slide carrier; arrows, to-and-fro movements; solid circles, raised studs for digital movement; horizontal and vertical strokes, mutual recesses—recessed faces of B and C face upwards.

is simple in design and cheap in manufacture, and can effect movement laterally, longitudinally or diagonally by digital manipulation, with one or both hands, without lag in adjustment such as that associated with geared thumb-screws. It could be useful in mass production for students.

The stage, originally constructed of "Opaloid", consists of a slide-carrier, for movement to and fro in one direction within a guide-frame on the microscope table; this guide-frame is separately mounted for movement to and fro upon the table, at right angles to the first-mentioned direction. The construction of the stage permits of calibration.

Each end-panel of the guide-frame is slidably disposed in a guide-member attached to the table of the instrument along its edge, each being equidistant from the focal aperture in the table. The guide-members with the guide-frame and slide-carrier, for convenience and economy, may be composed of light metal or synthetics.

Selected panels of the above-mentioned parts are recessed for the accommodation of the component parts of the stage, as indicated on the diagram (Figure I), these recesses being so arranged as to allow the slide to rest flush against the microscope table.

The slidable engagement between the slide-carrier and frame is such that the former may be readily inserted and withdrawn from the latter, whilst the frame may be slid out at either end from the guide-members. The guide-members may be attached to existing microscopes by the purchaser with the aid of an adhesive.

The slide drops directly into the slide-carrier, and can be displaced by a lateral movement of the guide-frame and an upward digital thrust against the slide.

This stage was inspected and commended by W. Watson and Sons, Limited, Makers of Microscopes, London, on October 31, 1946.

[1] Provisional patent 11822/47. Commonwealth of Australia. 1/5/47. *Re* "Improvements Relating to Microscopes".

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Management of the Patient with Headache", by Perry S. MacNeal, M.D., F.A.C.P., Bernard J. Alpers, M.D., Sc.D. (Med.), F.A.C.P., and William R. O'Brien, M.D.F.A.P.A.; 1957. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson, Limited. 7¾" × 5¼", pp. 148. Price: 38s. 6d.

The authors' aim is to provide a basic clinical understanding of the problem of headache and to discuss causes, differential diagnosis and treatment of the several types of headache.

"New Biology: 23", edited by M. L. Johnson, Michael Abercrombie and G. E. Fogg; 1957. Mitcham, Victoria: Penguin Books Proprietary, Limited. 7¼" × 4¼", pp. 128, with 16 illustrations. Price: 4s.

Contains six articles, including one on the mechanism of protein synthesis.

"Patients and Doctors: The Layman's Guide to Doctors and Doctoring", by Kenneth Walker; 1957. Mitcham, Victoria: Penguin Books Proprietary, Limited. 7¼" × 4¼", pp. 192. Price: 5s. 6d.

An exposition for the layman of the importance of the doctor-patient relationship.

"Report of an Investigation on Filariasis in the Berau Region (Inanwatan District, North-West New Guinea)", South Pacific Commission Technical Paper No. 105, by H. de Rook; 1957. Noumea: South Pacific Commission. 10" × 8", pp. 26, with illustrations and maps. Price: 2s. sterling.

The record of a detailed epidemiological investigation carried out in a remote area of Netherlands New Guinea.

"Atlas of Tumor Pathology" (Washington: Armed Forces Institute of Pathology). Section 8—Fascicle 30: "Tumors of the Kidney, Renal Pelvis and Ureter", by Balduin Lucké, M.D., Dr.P.H., and Hans G. Schlumberger, M.D.; 1957. 10¾" × 7½", pp. 208, with 199 illustrations. Price: $2.25. Section 10—Fascicle 36: "Tumors of the Pituitary Gland and Infundibulum", by James W. Kernohan, M.D., and George P. Sayre, M.D.; 1956. 10¼" × 7½", pp. 84, with 67 illustrations. Price: $1.00. Section 10—Fascicle 38: "Tumors of the Eye and Adnexa", by Algernon B. Reese, M.D.; 1956. 10¼" × 7½", pp. 208, with 132 illustrations. Price: $2.00.

Further fascicles in an outstanding series.

The Medical Journal of Australia

SATURDAY, SEPTEMER 7, 1957.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

A GUIDE TO AUSTRALIAN MEDICAL HISTORY: THE FIRST FEDERAL COUNCIL MEDICAL MONOGRAPH.

IT is fitting that the first monograph to be published under the Federal Council Medical Monograph Fund should be Bryan Gandevia's "An Annotated Bibliography of the History of Medicine in Australia". The history of both the science and the practice of medicine is of much greater practical importance than many people realize—as is history generally. The position was put admirably by the witty seventeenth-century divine, Thomas Fuller, in the following words (quoted by William Osler[1]): "Without history a man's soul is purblind, seeing only the things which almost touch his eyes."

Someone else has said that the only thing we learn from history is that we never learn from history. Be that as it may, we can, if we wish, learn a lot and find much to interest us in the study of medicine and its development in Australia. No comprehensive history of the subject has yet been written, and the task rapidly grows more difficult as medicine in Australia expands and early sources become more remote. In compiling this bibliography Gandevia has performed a signal service and to an important degree stopped the historical gap.

This work must have been a formidable task, but it has been well done. Some seven hundred items are included, each with a brief annotation, the vast majority having been seen by the bibliographer. His aim has been "to provide a widely representative rather than an exhaustive list", "a guide to the more readily available literature on Australian medical history". We wonder if much or anything of importance has been omitted within the terms of reference adopted, and are impressed by Gandevia's stated hope that the list is as comprehensive as possible in regard to the major Australian medical, historical and scientific journals, overseas medical and medico-historical periodicals, and separate publications. It is to be noted that the bibliography is intended to cover "medico-historical articles only and not original papers of historic significance"; on the other hand, it is stated that references to most of these will be found in one of the papers listed. This omission is a pity in some ways, although it is consistent with the bibliographer's intention. A few papers spring to mind that have an important place in the history of the science of medicine in Australia—for example, Swift's original paper on pink disease, Derrick's early studies on "Q" fever and Gregg's description of the congenital fœtal abnormalities associated with maternal rubella—but one wonders if there are enough of them to warrant separate compilation and if they might not have been better listed here. Perhaps a highly selective list might be considered for inclusion in any supplement to this bibliography which may appear in the future. However, this is a matter for the compiler to decide. The point is not intended as a criticism of an admirable piece of work, which should be welcomed by all who have an interest in the history of medicine in Australia and should be commended to all who have not yet realized the importance of the subject.

It is fervently to be hoped that the appearance of this bilbliography will stimulate those fitted to undertake it in the writing of the story of medicine in Australia in comprehensive form. This may be too great a task for any one individual, but might well be undertaken by a group, working together or as individuals, each taking responsibility for a section of the work. A discussion of the subject could well occupy the attention of the Section of the History of Medicine at the Congress next year in Hobart; indeed, it might provide a stimulus to this Section, which tends to lack much purpose and so unfortunately fails to arouse interest apart from the select few. The possibility of enlisting the aid of the Commonwealth Literary Fund might also be considered, as anything more than Gandevia's basic monograph would probably be considered outside the scope of the Federal Council Medical Monograph Fund.

What will be the next monograph published under the Fund remains to be seen. The appearance of this first monograph should stimulate further interest in the Fund and encourage financial contributions from those in the position to make them. The Fund could with advantage be brought again to the attention of the Branches of the British Medical Association in Australia and to other bodies interested in or related to the development of medical science. It is important that the Fund should be in the position to handle the worthwhile material that will inevitably appear as sound research work progresses in Australia.

[1] "Aequanimitas and Other Addresses", 1904, Lewis, London: 308.

Current Comment.

THE STORY OF HÆMATOLOGY.

HÆMATOLOGY is mostly thought of as a modern subject, and so it is, but behind it lies a long and interesting story. After several years of careful research into the subject, Camille Dreyfus[1] has condensed a wealth of valuable material into a small volume, which is not claimed to be anything like a complete survey of the history of hæmatology. Nevertheless, it does give a methodical and comprehensive selection of early discoveries considered to be well-defined landmarks along the road leading to a fuller development of this complex and all-important branch of modern medical science.

From a long experience and with special knowledge in this field of investigation, Dr. Dreyfus writes with the authority and conviction of the specialist. For many years he held the position of senior pathologist to the hospital of Saint Antoine in Paris, until a national crisis and a wave of anti-semitism forced him to seek refuge in the United States of America, where his special abilities were appreciated at Boston and later at the Mount Sinai Hospital in New York.

After a short foreword by the late Sir Lionel Whitby, who was then Regius Professor of Physic in the University of Cambridge, there is an introductory chapter, which contains the following sentence, indicative of the spirit underlying the writer's philosophy which is frequently stressed throughout the rest of the book:

> Overspecialization due to overcomplication of the tools we use is a trend of our time, although we are beginning to realize that clinical observation often has more to say than the microscope.

First in order comes the main chapter, which purports to afford "a glance at the history of the blood" from the days of Moses to the end of the nineteenth century, when the work of Paul Ehrlich and Georges Hayem already had provided the new science of hæmatology with a foundation upon which an unending series of anatomical, physiological, chemical, pathological and clinical systems were to be superimposed and knit more closely together in the next century. The chapter begins, unfortunately perhaps, with an unconvincing interpretation of ancient ideas concerning the blood and its alleged relationship to the soul. Stone Age people (quite rationally from their observations) endowed the visible blood with magical qualities as an elixir of life; while the invisible breath was associated in their minds with that universal spirit which animated and controlled all nature, whether animal, vegetable or mineral, and was concerned directly with the neolithic belief in immortality. In point of fact, knowledge of the blood remained at the prehistoric level until the dawn of the seventeenth century, when Galileo began to study nature with the aid of his telescope, and William Harvey worked out the essential details of the circulation by his patient application of the inductive method in scientific research. Then, the microscopists opened up an entirely new world with an instrument that "made a fly look as large as a sparrow" and for the first time the human eye perceived those minute "red particles" as they surged through the capillaries in the web of a frog's foot. Little progress was made in the science of hæmatology until the second quarter of the nineteenth century, when significant improvements in the microscope were the means of stimulating further interest and research. Dreyfus strictly observes chronological sequence, conciseness and clarity of expression in his scholarly exposition of these later developments.

The following three chapters deal with the successive steps taken by pathologists and clinicians in the second half of last century to elucidate the mysterious signs and symptoms observed in the blood diseases now recognized as chronic hæmolytic jaundice, leucocythæmia and *polycythæmia vera*. Galen in his time cleared the medical atmosphere with his explanations of the various essences elaborated in the blood, of which the most important derived its active principle from the general world spirit in the act of breathing. Recent work seems to indicate that the blood still holds hidden mysteries for scientists to unravel in the future.

The final chapter gives an illuminating outline of the life, work and scientific philosophy of Professor Georges Hayem, physician to Saint Antoine's Hospital, Paris, who collated and systematized the scraps of hæmatological data accumulated since Gabriel Andral and Alfred Donné began their studies over one hundred years ago, and used their influence to establish the microscope as an essential instrument of investigation in clinical medicine.

This small book is a scholarly contribution to a subject which has not previously engaged the concentrated attention of medical historians. It is fully documented with a list of references at the end of each chapter; and the illustrations, which include two plates of antiquated microscopes from the eighteenth century, are all helpful to an understanding of the text.

[1] "Some Milestones in the History of Hematology", by Camille Dreyfus, M.D.; 1957. New York and London: Grune and Stratton, Incorporated. 9" x 6", pp. 96, with illustrations. Price: $4.50.

GALACTOSÆMIA.

THE inborn error of metabolism, galactosæmia, was described by F. Goppert as long ago as 1917, but it is only during the past five years that extensive investigations have been made on the condition and the enzyme deficiency has been worked out. A. Holzel, G. M. Komower and V. Schwarz,[1] who have done much to elucidate the condition, have now reviewed their own and other workers' investigations.

Galactosæmia is characterized by a specific inability to metabolize galactose in a normal manner. The tissues are unable to convert galactose to glucose, and there result the accumulation of galactose in the blood, the passage of galactose in the urine and widespread tissue damage. The condition is relatively uncommon, but with increasing knowledge more cases are noted every year. The disorder may present itself in three grades.

In severe cases symptoms appear in the first few weeks of post-natal life. Vomiting and then jaundice and loss of weight are the earliest symptoms. The liver and sometimes the spleen enlarge greatly, and there may be ascites. Cataracts develop in more than half the cases. The children do not thrive. In the second group the development of symptoms is slow. Some months after birth, vomiting, difficulty in feeding and slow development are noted, and on examination of the child enlargement of the liver and often cataracts are found, but there is not acute illness. In the third group the symptoms are mild; the patients are not apparently ill, but they are happier when milk is not taken. They show an abnormal galactose tolerance on being tested.

In the first two grades proteinuria is usual, as also is aminoaciduria. Galactosuria, proteinuria and aminoaciduria all disappear when milk or lactose-containing foods are discontinued. When galactose is administered for a galactose tolerance test, hypoglycæmic symptoms frequently occur, and Holzel, Komower and Schwarz suggest that the test should be applied only when it is difficult to establish a diagnosis without its assistance.

The genetic aspects of the condition are far from clear. In every family examined by Holzel and his colleagues, one parent of a child with a definite condition of galactosæmia had an abnormally high galactose index, and in one case both parents were without any other clinical evidence of galactosæmia. The enzyme defect has recently been worked out. V. Schwarz, L. Golberg, G. M. Komower and A. Holzel[2] showed that the hereditary deficiency was to be found in the erythrocytes. The red cells of children

[1] *Am. J. Med.*, 1957, 22: 703 (May).
[2] *Biochem. J.*, 1956, 59: 22 (January).

with galactosæmia who had just had milk contained much galactose-1-phosphate but little glucose-1-phosphate. Holzer and his colleagues quote the more extended findings of H. M. Kalcar and his co-workers. The transformation involves three stages. Galactose with ATP is converted to galactose-1-phosphate; this with uridine-diphosphoglucose gives glucose-1-phosphate and uridine-diphosphogalactose. This last-mentioned substance is transformed to uridine-diphosphoglucose. In the subject with galactosæmia the enzyme for the last two reactions is missing from the body cells. The absence of this enzyme is not in itself the cause of the symptoms, for it is only when galactose or lactose is given that the symptoms appear. When all lactose and galactose are deleted from the diet, all symptoms disappear; and this is the accepted treatment.

This raises an interesting question. The cerebrosides contain galactose and are synthesized in the developing body. Many believe that the lactose which occurs in all mammalian milk is necessary to provide the galactose for this synthesis. If insufficient galactose is available, demyelinating conditions of the central nervous system may develop in later life. B. S. Platt[1] has suggested that infants fed on cow's milk may be in this condition. It seems more likely that the necessary galactose is synthesized in the tissues as required, for the necessary enzyme is present. This leaves unsolved the reason for lactose in the milk. Intolerance to milk in the diet is not uncommon, and it would seem worth while to determine whether persons showing this intolerance also show intolerance to galactose.

THE EARLY DIAGNOSIS OF GLAUCOMA.

THE importance of the early diagnosis of glaucoma needs no emphasis. Interest therefore attaches to a discussion of the subject by Sir Stewart Duke-Elder.[2] At the outset he lays down terminology in simple glaucoma and closed-angle glaucoma. In simple glaucoma the rise in ocular tension results from a physical blockage of the drainage of aqueous humour in its flow from the anterior chamber to the episcleral veins. Duke-Elder believes that simple glaucoma is initiated by a phase of vascular instability characterized by a periodic sympatheticotonia causing intermittent vasoconstriction; eventually the periodic functional change becomes a permanent organic vaso-obliteration, which involves a progressive condition of tissue sclerosis. If the vasosclerosis involves predominantly the posterior segment, cupping of the disk and field defects occur without any or with only a slight rise in tension (low-tension glaucoma); if the vasosclerosis is widespread, there is a combined effect. In early diagnosis an effort should be made to determine the onset of vaso-instability, sclerosis in the posterior segment and sclerosis in the anterior segment. The first is assessed by the presence of an abnormal diurnal pressure curve. A variation of more than five millimetres of mercury (Schiotz) is suggestive. The presence of sclerosis of the posterior segment is assessed by an analysis of its effect —*i.e.*, appearance of the disk, measurement of the visual field. The early signs to be looked for in the fields are a depression of the upper field, Roenne's nasal step and, most particularly, small scotomatous areas lying between the 10 and 20 circles in the upper part of the temporal field, initially not connected with the blind spot, but so placed that their extension would form the Bjerrum scotoma. The third objective—the detection of decreased facility of outflow of the aqueous at the angle—is performed by tonography. The test is also of importance in assessing treatment. The vasomotor element in simple glaucoma is most logically treated by miotics, embarrassment of the drainage by surgery. So long as facility of drainage is normal, treatment by miotics is safe, and wiser than surgical intervention; as soon as facility of drainage becomes abnormal, then surgery should be considered. The water-drinking test is valuable if the result is positive, but in early cases a negative result is not helpful. Other provocative tests are so unreliable in early glaucoma that their use is not justified.

In closed-angle glaucoma, Duke-Elder states, rises in ocular tension are due to a closure of the angle of the anterior chamber by approximation of the root of the iris to the trabeculæ and the periphery of the cornea. The anterior chamber is shallow, the lens is disproportionately large, the lens iris diaphragm lies well forward, and the angle of the anterior chamber is narrow. The commonest underlying cause of the raised tension is a condition of vasomotor instability, which leads to periodic rises in tension in the small blood vessels of the uveal tract, so that an excess of fluid is passed into the posterior chamber. The diagnosis of closed-angle glaucoma in a phase of raised tension is easy. Diagnosis between attacks is difficult; it is dependent on an assessment of the patient and his history, an adequate examination of the eye and, finally, if necessary the performance of a provocative test.

[1] *Brit. M. J.*, 1955, 1:179 (January 22).
[2] *Tr. Ophth. Soc. U.K.*, 1956.

SOME RECENT OBSERVATIONS ON LATHYRISM.

LATHYRISM has been the subject of many apparently unrelated clinical observations and experimental investigations. Hans Selye[1] has now attempted to correlate the scattered information, and he supplies a good deal of the experimental data, much of which has not previously been published. He divides lathyrism into neurolathyrism and osteolathyrism. Neurolathyrism, which occurs mainly in young men and domestic animals, is caused by a diet predominating in certain pulses (lathyrus species) and is manifested chiefly by spastic paraplegia and ocular symptoms. Osteolathyrism does not cause any clear-cut syndrome in man, and it was recognized as an entity only in 1933 when Geiger, Steenbock and Parsons found that rats fed on diets rich in the seeds of sweet peas (*Lathyrus odoratus*) developed deformities in the long bones, spinal curvature, distortion of the thoracic part of the skeleton and herniæ.

The toxic agent in the various types of lathyrus are certain nitriles. The most effective substance in producing osteolathyrism is aminopropionitrile, which does not occur in the lathyrus species. The defect seems to be in the metabolism of organic sulphur, resulting in defective formation of chondroitin sulphate. Although neurolathyrism has not been experimentally produced, there is a neurological syndrome which can be induced by certain aminonitriles. These disturbances are characterized by excitement, with choreiform and circling movement (ECC-syndrome) as well as severe ocular lesions. One nitrile which produces mild osteolathyrism has been shown to sensitize the rat to the production of ECC-syndrome by another and vice versa. This suggests that there is some pathogenetic relationship between osteolathyrism and the ECC-syndrome in the rat. Selye was able to show that the development of osteolathyrism depended largely upon conditioning factors of stress and hormonal balance. Somatotrophic hormone and thyroid deficiency facilitated the development of skeletal lesions, while ACTH, cortisone and thyroxin had the opposite effect. The bone abnormalities which were induced in the rat resembled those of certain spontaneous human disorders, such as the formation of exostoses, Perthes's disease, kyphoscoliosis, and degenerative arthritis amongst others. In the rat dissecting aneurysm may accompany the lesions of osteolathyrism. In man dissecting aneurysm has often been observed to be accompanied by skeletal deformities. These facts must make one wonder just how far our dietetic environment is responsible for disorders of the skeleton and for dissecting aneurysm.

[1] *Rev. canadienne de biologie*, April, 1957.

Abstracts from Medical Literature.

HYGIENE.

Combined Diphtheria - Pertussis - Tetanus Antigen plus Poliomyelitis Vaccine.

P. L. KENDRICK AND G. C. BROWN (*Am. J. Pub. Health*, April, 1957) have studied the serological responses of guinea-pigs and monkeys to triple diphtheria, pertussis and tetanus vaccine (DPT), poliomyelitis vaccine, and combined triple and poliomyelitis vaccine (DPT-P). All antigenic components, in whichever vaccine they were given, stimulated demonstrable antibodies. In the present experiments with limited numbers of animals, the diphtheria and tetanus antitoxin levels in guinea-pigs were somewhat lower after the combined DPT-P vaccine than after triple DPT vaccine; also, the poliomyelitis response was less after combined DPT-P vaccine than after poliomyelitis vaccine alone. In monkeys, however, all antibody levels appeared to be somewhat higher after the combined product than after poliomyelitis vaccine alone. The pertussis serological response in both guinea-pigs and monkeys was consistently good, regardless of the combination in which it was given; also, in pertussis mouse-protection tests, the DPT and DPT-P vaccines were found to be of similar potency. The authors consider that the results encourage further work with combined multiple antigens in which poliomyelitis vaccine is included.

Field Trial of Typhoid Vaccines.

B. B. CVJETONOVIC (*Am. J. Pub. Health*, May, 1957) carried out carefully controlled field trials on the effectiveness of typhoid vaccines in an area inhabited by 100,000 people in Jugoslavia. The results of the trials show that a vaccine effective against typhoid fever in man can be produced, that a phenolized vaccine is superior to an alcoholized vaccine as a protection against typhoid, that the latter produces a significantly higher V_1 titre than the former, and that the results of potency tests of vaccines in animals are not comparable with field results in human beings. The author concludes with a statement that the carrying out of controlled field trials of prophylactics is the most rapid and exact and often the only way to the solution of many problems of prevention of communicable diseases.

Fluoride in Domestic Water and Periodontal Disease.

A. L. RUSSELL (*Am. J. Pub. Health*, June, 1957) has investigated the effect of varying amounts of fluoride in domestic water supplies on the periodontal tissues of people who drink the water. Residents of three communities supplied for from seven to forty-four years with water containing fluoride were examined, and the condition of their periodontal tissues was noted. The results were compared with those obtained in similar areas where the water contained practically no fluoride. The periodontal tissues of the former were found to be healthier than those of the latter. In a second series of examinations, children from areas where they had all their lives drunk water containing fluorine were compared with children who had recently immigrated to the same areas. There was a tendency for the periodontal health of children in the first group to improve, relative to that of migrants, as their advantage in water-borne fluoride consumption increased. Most of the differences were slight and not sufficient to support a hypothesis that the use of water containing fluoride results in healthier periodontal tissues. However, there was no evidence that fluoride in water harmed the periodontal tissues.

Grand Rapids Fluoridation Study.

F. A. ARNOLD (*Am. J. Pub. Health*, May, 1957) summarizes observations made of the Grand Rapids water fluoridation study for the past eleven years. The results of this study, together with others which have been conducted for similar periods, indicate the feasibility of this procedure for the control of dental caries. In all studies the findings show a reduction of 60% to 65% in the prevalence of caries in the permanent teeth of children born subsequent to the change in water supply. Furthermore, the evidence strongly suggests beneficial effects on teeth which were formed, or had erupted, prior to the initiation of water fluoridation. Results to date show a slight increase in dental fluorosis which is of no public health significance. No scientific evidence has been produced by any of the studies to suggest that water fluoridation, at levels recommended for caries control, has any adverse effect on any other part of the body.

Observations on Natural Poliomyelitis Virus Infections in Immunized Children.

H. M. GELFAND, J. P. FOX AND D. R. LE BLANC (*Am. J. Pub. Health*, April, 1957) have investigated the serological response one month after the second injection of Salk poliomyelitis vaccine in 300 incompletely immune members of 118 Louisiana households. They found that the type 3 component of the vaccine was the least antigenic and that the de-novo response to a particular type of antigen was increased by the preexistence of heterotypic antibody. Alimentary infections with poliomyelitis viruses in the same group before and after vaccinations were also compared. The comparison indicated that two doses of Salk poliomyelitis vaccine did not materially influence the frequency or duration of alimentary infection or the amount of virus excreted in the fæces. The authors conclude that extended use of killed virus vaccines will not result in the gradual elimination of poliomyelitis viruses from vaccinated communities as has occurred in the case of the smallpox virus.

Pasteurization of Milk Containing the Organism of "Q" Fever.

J. B. ENWRIGHT, W. S. SADLER AND R. C. THOMAS (*Am. J. Pub. Health*, June, 1957) present the results of an investigation into the resistance to heat of *Coxiella burneti* in milk. Laboratory thermal-resistance studies show that heating *C. burneti* suspended in whole raw milk for 30 minutes at 143° F. will not eliminate all the viable rickettsiæ, but heating at 145° F. for 30 minutes will. Similar results were obtained when a vat-type commercial pasteurizer was used. The results produced by a high-temperature, short-time type of commercial pasteurizer tend to confirm the extrapolation of laboratory derived data, and support the standard of pasteurization of 161° F. for 0·15 second as adequate to destroy all viable *C. burneti* in whole raw milk.

SURGERY.

C-Reactive Protein in Patients After Operation.

M. RAPPORT, A. SCHWARTZ AND L. GRAF (*Ann. Surg.*, March, 1957) state that C-reactive protein (CRP) is a beta globulin which is not detectable in normal blood but appears in certain inflammatory conditions associated with tissue breakdown. They have studied the serum levels of C-reactive protein in 33 patients after various surgical procedures. In most of these patients the amount of CRP increased rapidly within the first two or three days and then declined until it completely disappeared from the serum some two weeks after operation. The height of the CRP level appeared to be related to the degree of trauma involved. After extensive operations, CRP was not observed until six or eight hours after initiation of the procedure. The authors consider that the CRP is a manifestation of activity of cells which are produced in early response to tissue injury such as macrophages or perhaps polymorphonuclear leucocytes. They consider that the time relation of its appearance indicates that CRP response is not related to cellular mechanisms resulting in the formation of antibody, a fact which they consider consistent with its lack of specificity.

Surgery Under Hypothermia for Severe Hepatocellular Disease.

W. BERNHARD, G. CAHILL AND G. CURTIS (*Ann. Surg.*, March, 1957) produced a lethal period of hepatic hypoxia (60 minutes) in two groups of dogs by temporary occlusion of the hepatic artery, portal vein, cœliac axis and superior and inferior mesenteric arteries. In the first group, the period of ischæmia was produced in normothermic animals, but in the second group the occlusion period was produced after the induction of hypothermia (25° to 31° C.). The presence of hepatic damage in all animals was determined from examination of serial biopsies of the liver performed before, during and after the occlusion period. In each of these biopsies, quantitative determination of changes in hepatocellular glycogen, glucose and lactate was performed. Selective staining techniques were used on the specimens to demonstrate any alteration in the location and quantity of glycogen within hepatic lobules. This period of hepatic anoxia produced a profound hypotension in the normothermic dogs, resulting in marked

pulmonary, hepatic and gastro-intestinal congestion. The mortality in this group was 100%. Glycogen depletion was noted quantitatively and histologically in these animals and was accompanied by an elevation in the intracellular content of glucose and lactate. The hypothermic dogs survived the period of occlusion without evidence of hepatic damage. The authors consider that the clinical applications of this experiment are that hypothermia should be used in patients with marked cirrhosis, portal hypertension and œsophageal varices which necessitate a decompressive shunt operation, and that it should be used to facilitate the surgical control of actively bleeding varices—as it would diminish the hepatic damage consequent on hypotension, anoria or prolonged periods of anæsthesia. They also consider that hypothermia would make feasible the resection of primary or metastatic hepatic tumours in a dry operating field during temporary hepatic vascular occlusion.

Peptic Ulcer Therapy.

W. WALTERS (*Arch. Surg.*, April, 1957) has made an evaluation of peptic ulcer therapy from the surgical standpoint, based on the follow-up investigation of patients operated on at the Mayo Clinic between 1945 and 1950. He considers that the Billroth II type of gastric resection (two-thirds to three-quarters resection) for chronic recurring duodenal ulcer gives the best results for men and women, as measured by the relief of symptoms, the functional results which have followed, and the low incidence of recurrence of ulcer. When a similar amount of stomach was removed and a Billroth I operation was performed, the functional results were not so much superior to those of the Billroth II operation as to overcome the disadvantages of a two and three times incidence of recurring ulceration; this was true regardless of the sex of the patient. In the treatment of gastro-jejunal ulcer developing after gastro-enterostomy, although the Billroth II type of gastric resection with removal of the gastro-jejunal ulcer and the gastro-enteric stoma gave results superior to those that followed the Billroth I type of gastrectomy, vagotomy in certain but fewer cases has given excellent results. In chronic recurring gastric ulceration, the results of both the Billroth I and the Billroth II resections were about the same. The author considers that there is a place for gastro-enterostomy in certain types of large, penetrating, obstructional duodenal ulcers, especially in patients with low or average amounts of gastric acid or in elderly patients with burned-out sclerotic ulcers and low amounts of acid. However, the long-term results of such a procedure, even when vagotomy has been added, have not compared favourably with those of partial gastrectomy. In such cases—that is, after gastro-enterostomy and vagotomy—the incidence of recurrent ulcer was four times that observed after partial gastrectomy. The author also found, when comparing results of gastrectomy and gastro-enterostomy with vagotomy, that the functional results of the latter presented many unpleasant post-operative sequelæ which were not present with the former; whilst the incidence of dumping disturbances or disturbances of nutrition was about the same in the two groups, regardless of sex.

Duodenal and Jejunal Diverticula.

H. ELSTNER AND J. WAUGH (*Surgery*, April, 1957) state that increasing numbers of duodenal and jejunal diverticula are being demonstrated radiologically. The majority of diverticula are asymptomatic; but even when symptoms are present, a thorough search must be made for associated pathological states. The symptoms referable to these diverticula may be varied and complex. Surgical procedures are best reserved for the management of complications and incapacitating symptoms. Resection with end-to-end anastomosis is the procedure of choice in the surgical treatment of jejunal diverticula, and total removal is preferred to inversion or side-tracking procedures in the treatment of duodenal diverticula. Removal of a duodenal diverticulum may be a hazardous operation, especially when the diverticulum is adjacent to the ampulla of Vater. Injury to the ampulla with interference with drainage of bile or pancreatic secretions may lead to pancreatitis. The development of duodenal fistula is another factor which is responsible for high mortality and morbidity. Benefit is achieved from the surgical treatment of duodenal diverticula in little more than 50% of the cases.

Treatment of Duodenal Ulcer.

T. EVERSON, V. HUTCHINGS, J. EISEN AND M. WITANOWSKI (*Arch. Surg.*, April, 1957) state that the relative merits of partial gastrectomy and vagotomy with gastro-enterostomy in the definitive surgical treatment of duodenal ulcer remain a controversial subject at the present time. During the period 1946 to 1954, a total of 348 patients with duodenal ulcers were subjected to partial gastrectomy (Billroth II type), and 178 patients with duodenal ulcers were subjected to vagotomy with gastro-enterostomy on the surgical services. One or more post-operative complications occurred in 37·7% of the patients after partial gastrectomy and in 25·8% of the patients after vagotomy with gastro-enterostomy. The post-operative mortality after partial gastrectomy was 4·9%, as compared with 1·1% after vagotomy with gastro-enterostomy. When the principal indication for surgery was pain, the post-operative mortality was 0·9% after partial gastrectomy and 1·1% after vagotomy with gastro-enterostomy. The commonest cause of death after partial gastrectomy was duodenal stump leak, accounting for seven of 17 cases. Recurrent ulceration, proved at surgery and/or by X-ray examination, was noted in 2·2% of 231 patients followed after partial gastrectomy and in 7·6% of 131 patients followed after vagotomy with gastro-enterostomy. In addition, presumptive recurrent ulceration (hæmatemesis and/or characteristic ulcer pain) was noted in 1·7% of the patients studied after partial gastrectomy and in 5·3% of patients studied after vagotomy with gastro-enterostomy. No significant difference was noted in the percentage of patients below average healthy weight after partial gastrectomy and after vagotomy with gastro-enterostomy, or in the incidence of the dumping syndrome after partial gastrectomy. Of the surviving patients, 92·6% followed after partial gastrectomy and 84·0% followed after vagotomy with gastro-enterostomy were satisfied with the operative result. However, when those patients who died after the operation were included among dissatisfied patients, patient satisfaction was 86·3% after partial gastrectomy, as compared with 82·7% after vagotomy with gastro-enterostomy.

Problems of Soft Tissue Calcification.

H. MCCARROLL (*Arch. Surg.*, April, 1957) states that, in the light of present knowledge, problems of abnormal soft tissue calcification are probably related to the over-all problems of collagen diseases, and result from primary degenerative changes in connective tissues. He considers that *calcinosis universalis* represents widespread calcium deposition in fibrous or connective tissue structures in which degenerative changes have resulted from a systemic disease process. In other more localized types of soft tissue calcification, primary degenerative changes may serve as the etiological factor, but many of these result from trauma to tendinous or fibrous tissue structures.

Ano-Rectal Carcinoma of Extra-mucosal Origin.

Y. ZIMBERG AND S. KAY (*Ann. Surg.*, March, 1957) state that the literature contains many reports of neoplasms that involve primarily the tissues adjacent to the ano-rectal canal. They consider that the anal glands are a logical source for many of these malignant conditions. The difficulty of diagnosing these conditions is that the signs and symptoms are varied and frequently mislead the observer to the diagnosis of an inflammatory condition; so that any perianal inflammatory condition which does not yield quickly to correct treatment should be investigated from the point of view of a malignant condition, deep biopsy being performed. The authors report three new cases of extramucosal ano-rectal neoplasm and state that a rational operation for these conditions, despite the degree of late involvement of mucous membrane, should consist of a wide abdomino-perineal resection of the ano-rectal canal with the inclusion of the pelvic fascia, iliac and hypogastric lymphatics and nodes and at times bilateral dissection of the inguinal regions.

Intramural Duplications of the Œsophagus.

H. MAIER (*Ann. Surg.*, March, 1957) reports a case of intramural duplication of a segment of the thoracic œsophagus which first caused dysphagia in adult life. In the upper third of the thoracic œsophagus there was a double-barrelled lumen, but one of the channels had a blind lower end. This condition was diagnosed correctly by the radiologist. The author discusses the surgical treatment of this rare type of duplication by transthoracic and transœsophageal division of the congenital vertical partition within the œsophageal lumen.

Brush Up Your Medicine.

THE USE AND MISUSE OF PLASTER CASTS.

WHEN plaster of Paris became available, it was possible to apply surgical principles in the treatment of fractures much more effectively than ever before. With plaster one is able to hold the fracture and at the same time allow full movement of those joints that need not be immobilized. For example, compare the way in which a patient with a well applied cast for a Colles's fracture can move his fingers fully with the plight of a similar patient treated in one of the old splints made of wood, aluminium or even newspaper. As a result of this improved fixation it has become possible to start rehabilitation of the fractured limb from the very onset of the injury and not to wait until union of the fracture has occurred. This concept of early rehabilitation is probably the most important recent advance in the treatment of fractures, and it is doubtful if it could have been developed without the use of plaster of Paris. As a result of this change women with broken arms are urged to continue doing their housework while in plaster; and if they do, the complications of stiff fingers, stiff wrists and stiff shoulders do not arise. Men with broken legs and ankles can usually remain at selected duties and even play a little golf. People with broken necks and spines are kept ambulant and active, and are thereby prevented from developing the anxiety states which can so easily complicate this type of injury.

Plaster has in fact become so useful that we sometimes forget its limitations. There is a tendency moreover to believe that every fracture must be treated in plaster. In some fractures immobilization is not necessary; in many cases it is effective only when applied in a definite way, and in others it is a potential source of danger to the circulation of the limb.

Plaster casts are used in the treatment of fractures mainly to immobilize the fragments until bony union has occurred—for example, in a broken tibia—and occasionally to protect a damaged area and relieve pain—for example, in a fractured *os calcis*. For many fractures, however, it is unnecessary and unduly uncomfortable. For example, a man with a crush fracture of the great toe does not need special immobilization, and he will be much more comfortable in a slipper than in a plaster cast. The same is true of most fractures of the foot. Although a fracture of the waist of the navicular must be immobilized in a plaster cast until union is complete, no fixation is needed for a fracture of the tuberosity of the navicular and for most other fractures of the carpus. Many fractures of the elbow are held firmly when the joint is flexed and the wrist supported in a collar and cuff. To increase this fixation a shoulder spica is needed, but a plaster cylinder, so often used, does nothing to help immobilization. In treating compression fractures of the spine there has been a marked change from the days of trying to fix the spine in hyperextension. No splintage is needed for most fractures of the thoracic and lumbar vertebræ, and where some support is considered advisable it can be more effectively and much more comfortably applied by wearing a simple Taylor brace than a plaster jacket.

The actual application of the cast raises many points. Generally it is necessary to immobilize the joint above and below the fracture site, but this is not a hard and fast rule. It is not true of a Colles's fracture, and in fractures of the forearm and leg it is useless unless the proximal joint is fixed in flexion so as to prevent rotational stresses from being passed on to the fracture site. In some cases, to immobilize the joint distal to the fracture and not the proximal one is worse than useless—*e.g.*, a long arm plaster cast in treatment of fractures of the shaft of the humerus. This does nothing to fix the fracture, and with the bone support gone and the muscles soon exhausted by the weight of the plaster cast the limb is often supported only by the nerves and vessels. There is no need for proof of this statement. Hundreds of such fractures were treated in this way in the early years of the last war, and many men later had their arms amputated at base hospitals because the circulation to the limb had failed. Later an instruction was given to fix these plasters to the trunk by a modified shoulder spica, and these tragic complications disappeared.

Plaster casts can lead the surgeon into a state of false security. For example, even after a fracture has been reduced and surrounded in a plaster cast redisplacement will often occur. A child in a hip spica can develop an adduction deformity of the hip to everyone's amazement, and most plaster jackets that leave the legs and arms free are more of a discomfort to the patient than a protection to his spine. Fractures which tend to undergo displacement should have their plasters moulded on the three-point system and not just left in a circular cast. A hip joint which tends to adduct needs a double hip spica and often traction on the affected leg. A spine can be more effectively protected by a light brace which holds the shoulders firmly and keeps the back extended.

The foregoing considerations, however, are not nearly as important as the inherent danger to the circulation of a limb when it is encased in a plaster cast. There is a tendency to concentrate on the position of bony fragments as seen in X-ray films and to forget the state of the soft tissues. The commonest and severest complications of fractures treated in plaster are not due to malunion or non-union, but are associated with interference with the circulation. For example, bad functional results following a Colles's fracture are nearly always due to stiff wrists and stiff fingers and not to some residual deformity. In nearly all such cases the basis of the trouble has been a tight plaster cast which has caused swelling and œdema of the digits to occur. Once this has happened full movement may never be restored. Such fractures should never be treated in an encircling cast until the initial swelling has subsided. In the lower limb the dangers are less often realized, but are equally far-reaching. A tight plaster may cause complete obstruction to the posterior tibial artery or more commonly partial ischæmia to the calf muscles. In the first case gangrene will develop and lead to amputation. Such damage can be caused in the first few hours, when a critical circulation, already injured at the time of the accident, is trying to reestablish itself. To split or remove the cast on the following day is of no avail. Muscles can survive only for about six hours when deprived of their blood supply. More often the ischæmia is not so complete, but it causes some fibrosis of the main muscle bellies, and this may not be realized. The initial swelling subsides, and the patient becomes comfortable. When the fracture has united, and the cast is finally removed, it is noted that the patient has marked stiffness of the ankle and tarsal joints with clawing of the toes and much wasting of the calf. Recovery in such cases is very slow and often incomplete. Although these findings are usually attributed to the long period for which the leg has been immobilized, I believe that they are almost invariably due to ischæmia. In many cases this ischæmia has been caused by a tight plaster cast, and the damage has been done within a few hours of its original application. The danger to the circulation is always present when any encircling bandage like plaster is applied to a limb, but the danger is greatest in certain fractures—*e.g.*, supracondylar fractures of the humerus and fractures of the upper third of the tibia. In the former group plaster casts are never necessary; and when they are used in the tibial cases, the surgeon must not attempt to manipulate the fragments while the plaster is setting. Reduction must be first obtained, by traction from assistants, by skeletal traction or even by internal fixation, before the limb is immobilized. When there is a chance of ischæmia developing, the limb should be padded, and the whole length of the plaster cast should be split as soon as it dries. Although every effort must be made to secure accurate reduction of fractures, it must be remembered that the circulation to the limb and the control of any infection present are more urgent and more serious considerations.

Summary.

Some aspects of the use and misuse of plaster casts, especially in the treatment of common fractures, have been discussed.

It has been pointed out that some fractures do not need immobilization at all, and that others are better treated without plaster fixation.

The dangers of tight plaster casts have been stressed. Complete obstruction of the circulation may lead to gangrene and amputation, but more commonly partial ischæmia causes stiff joints and much residual disability.

Provided, however, the danger to the circulation of the limb is appreciated, plaster of Paris casts are still the best form of fixation for most fractures, and they allow rehabilitation of the limb to be started from the onset of the injury.

HUGH C. BARRY, F.R.C.S. (Eng.), F.R.A.C.S.

Sydney.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

MEDICAL DEGREES FOR LADIES.

[From the *Australasian Medical Gazette*, March, 1887.]

AT a meeting of the Council of the University of Melbourne on February 21 it was decided by a large majority to admit ladies as students of medicine. We are pleased to say that there were only three dissentients to this course but must express our regret and surprise to find that these gentlemen were Drs. Brownless and Cutts with Mr. Ellery.

We are of opinion that women should be allowed to follow any calling for which they are fitted and no one but a narrow minded individual would deny that medicine is one of them. They should be granted every facility for being thoroughly trained for the calling they take up, and when they enter into competition with men, should receive no advantage and be under no disadvantage on account of their sex.

We cannot too highly congratulate the Melbourne University on the marked advance in the liberality of ideas possessed by its present governing body when compared with the actions taken by that holding sway in 1871 when the sister of the editor of the A.M.G. was refused leave to matriculate in Arts, she having been one of the first two ladies to pass the matriculation examination. Her demand for matriculation was met by a simple refusal, any explanation of the reasons for such refusal other than the fact that the University did not choose to give degrees to ladies, being declined to be given.

In Sydney there are already lady medical students attending lectures and going through the usual medical course. Steps are also being taken to establish a college for women to be affiliated with that University.

Correspondence.

CONTACT DERMATITIS FROM 18-CARAT GOLD.

SIR: The case reported by Dr. Chenoweth (M. J. AUSTRALIA, July 6, 1957), prompts this letter, if only because of his opening remarks. Possibly the "rarity of commercial gold as an allergen" is purely relative; that is, every single substance incriminated as the cause of a contact dermatitis does not get written up in the journals — except that it be of a particularly unusual character.

Within the past few months I have come across three such cases: two, my own patients, one the patient of a colleague. All three cases were married women, and in each case the dermatitis was associated with rings of 18-carat gold.

Mrs. X, aged thirty-two years, presented with a four-week history of an irritable rash under the wedding-ring. She was prompted to seek treatment by the appearance of an identical rash under a signet-ring worn on the right hand. Examination showed an acute dermatitis with vesiculation and spreading erythema on the left ring-finger, extending for half an inch; an identical condition was present on the right ring-finger, but only extending about a quarter of an inch. She had noticed a certain remission after leaving her rings off for a couple of days, but as she has two children she was somewhat reluctant to do this when she left the house. After a few days' treatment with "Stérosan-Hydrocortisone" ointment, leaving the rings off, the condition vanished. After about four weeks' freedom (still wearing the rings again) the rash started to return. However, as this was not entirely unexpected, the above ointment was used at the very first sign, and the condition did not develop. She still wears her rings and has been free for three weeks. She is instructed to apply the ointment at the first sign of a return of the rash.

Mrs. Y, aged twenty-eight years, presented with an identical condition three weeks ago, to a much milder degree and only under the wedding-ring. For the same reason as in the first case she avoided completely removing her ring. It cleared with two days' treatment with the above ointment, and so far has not returned, in spite of still wearing the ring.

The case treated by my colleague was essentially similar, of a severity between my two cases, responding to the same treatment.

Hence it appears that commercial gold is not such a rare allergen as your contributor assumes.

Yours, etc.,

Wilstrasse 88,
Dübendorf/ZH.,
Switzerland.
August 17, 1957.

R. GRAEME CAMERON.

SIR: I appreciated Dr. Bruce Robinson's interest in this case (M. J. AUSTRALIA, July 6, 1957) and his query as to the patient's domestic situation at the appearance of the rash five years previously at the site of her wedding ring.

The lady was a happily married woman with no domestic worries and with healthy outside interests. Since removal of the gold contacts nine months ago and the substitution of a platinum wedding ring, her skin has been quite free of inflammation.

Yours, etc.,

71 Collins Street,
Melbourne,
August 30, 1957.

ERNEST CHENOWETH.

PSYCHIATRIC CONSEQUENCES OF RAUWOLFIA THERAPY.

SIR: While most psychiatrists would agree with Dr. Kyneur (M. J. AUSTRALIA, August 17, 1957, page 241) that depressive states are a not uncommon complication of long-continued administration of rauwolfia preparations, many would consider that his is a rather gloomy view of the matter.

My impression is that administration of small doses of methyl-amphetamine or dextro-amphetamine with rauwolfia does away with the depressive side effects in the majority of cases. Some well-established depressive states require electroplexy, and I have yet to see one that has not responded to this treatment in the usual time of two to three weeks.

Again, while agreeing that administration of rauwolfia should be carefully controlled and that clinicians should be aware of and watchful for side effects, Dr. Kyneur's paper could be misleading. This applies especially to the statement that rauwolfia induces insanity in normal people. It is doubtful whether depression occurs in more than a very small proportion of the patients in whom it is used. It is even more doubtful whether it should be classified as a psychotic state. My impression is that it usually resembles an intense neurotic depression.

Finally, this depressive state is not to be confused with the hallucinatory schizophrenia-like psychoses that are almost invariably produced by mescaline and lysergic acid diethylamide.

Yours, etc.,

21 Rae Street,
Hawthorn,
Victoria.
August 23, 1957.

L. H. WHITAKER.

SIR: Through the courtesy of your Journal, I would like to draw attention to certain matters arising out of Dr. F. J. Kyneur's article in THE MEDICAL JOURNAL OF AUSTRALIA of August 17, 1957, entitled "Psychiatric Consequences of Rauwolfia Therapy".

The therapeutic experiences of rauwolfia therapy and its side effects have been widely reported from most countries in the world. I know that recently Ciba has conducted a world-wide investigation of the use of "Serpasil" amongst general practitioners; this survey included Australia. The results have yet to be published and will, no doubt, give clear-cut information. From my own experience it is apparent that side effects have not in any way outweighed its therapeutic usefulness in certain types of hypertensive disease. As with most effective drugs, there are minor side effects experienced by some, and in certain instances

mental depression and its consequences have occurred. However, the question remains as to whether or not this is a direct effect of rauwolfia therapy. According to Mayo Clinic investigators, (Litin *et alii*, 1956) the evidence indicates that rauwolfia *per se* does not cause depression, but rather that it unmasks an underlying susceptibility to depressive reactions. When such reactions occur, they are heralded by change of sleep pattern, an inability to get started, especially in the morning, and an alteration of the patient's spirits, long before serious depression occurs. Every practitioner can weigh the anti-hypertensive merits of this drug against such an occasional incident of this nature, which can be recognized and indicates a suspension of any rauwolfia therapy.

It is unfortunate that the lay publicity given to this matter may disrupt the effective use of these compounds, though possibly sparing a few from a complication which can be recognized and prevented.

Real hypertensive disease and its associated complications still account for an increasingly high mortality rate. Any therapeutic agent which is effective against this is an advance which should be preserved and its side effects watched for with vigilance.

Yours, etc.,

225 Macquarie Street, Sydney,
August 27, 1957.

FRANK L. RITCHIE.

Reference.

LITIN, E. M., FAUCETT, R. L., and ACHOR, R. W. P. (1956), "Depression in Hypersensitive Patients Treated With Rauwolfia Serpentina", *Proc. Staff Meet., Mayo Clin.*, 31: 233 (April 18).

WILLIAM HARVEY AND COFFEE.

SIR: I find in "The Saga of Coffee", by H. J. Jacob (George Allen & Unwin Ltd., London) a reminiscence on William Harvey (page 128):

> When William Harvey (1578-1657) was nearing his latter end, he summoned a solicitor and showed the man of law a coffee-bean. Thrusting his fingernail caressingly into the groove of the bean, he said with a smile: "This little fruit is the source of happiness and wit". In his will, he bequeathed to the London College of Physicians the greatest treasure in his laboratory, fifty-six pounds of coffee, directing that his colleagues, so long as the supply lasted, should assemble, month by month, to commemorate the day of his death by drinking coffee together . . . .

Harvey never dreamed that twenty years after his death London would be full of coffee-houses; or that coffee, of which he had procured a sack from Venice at great cost, would then be brought to England in shiploads, to fill the warehouses at the docks.

Yours, etc.,

15 Isabella Grove, Hawthorn, Victoria.
August 23, 1957.

H. GOLDBERG.

A TRIBUTE TO LORD NUFFIELD.

SIR: I am writing to you on behalf of a small group of medical men, the signatories of the attached letter, to ask you whether you would be so kind as to print the letter in an early issue of your journal, and so help us to give an opportunity to doctors in your country of contributing towards a fund which we believe that many of them will wish to support.

We are convinced that doctors throughout the Commonwealth will welcome this opportunity of doing honour to Lord Nuffield on his eightieth birthday. Here, in the United Kingdom, a personal letter is being sent to every doctor. But it is impossible for us to write individually to doctors overseas; and so we are dependent for reaching them upon the kindness of the editors of the medical journals which they read.

If you can help us in this way, we shall indeed be grateful.

Yours, etc.,

CLEMENT PRICE THOMAS,
President,
The Royal Society of Medicine.

DEAR DOCTOR,

On October 10 next, Lord Nuffield celebrates his eightieth birthday. As is well known, Lord Nuffield is the greatest benefactor to medicine this country has ever known, and there can be few medical men and women who have not benefited, directly or indirectly, from his gifts.

It seems fitting to us that, on the occasion of his eightieth birthday, members of the medical profession should have an opportunity of showing the regard which they have for Lord Nuffield, and their gratitude for his far-sighted generosity.

With this in mind, we write to ask you to contribute, however modestly, towards a birthday present which we propose to give Lord Nuffield as a tribute from the profession, both at home and in the Commonwealth, at some celebration to be held in London or in Oxford near the date of his birthday.

It is our intention to buy a present for Lord Nuffield from the money subscribed, and to give him the balance to use as he wishes.

A maximum donation of about two guineas is suggested, but any amounts, either larger or smaller, will be very acceptable. Donations of even a few shillings would be welcome, for the important thing is that Lord Nuffield should know that the present comes from the profession as a whole.

We earnestly ask you to send a contribution.

Cheques and postal orders should be made payable to the Nuffield Birthday Fund, and sent to 1, Wimpole Street, London, W.1., as early as possible.

Yours sincerely,

W. RUSSELL BRAIN,
HENRY DALE (Trustee),
EVANS,
R. R. MACINTOSH,
W. N. PICKLES,
HARRY PLATT,
ARTHUR PORRITT,
CHARLES D. READ,
CLEMENT PRICE THOMAS (Trustee).

1 Wimpole Street,
London, W.1,
August, 1957.

MATERNAL AND FŒTAL PROGNOSIS IN TOXÆMIAS OF PREGNANCY.

SIR: May I comment on one paragraph of the fine article contributed by my good friend Professor F. J. Browne in THE MEDICAL JOURNAL OF AUSTRALIA of August 10, 1957, at page 198, entitled "Maternal and Fœtal Prognosis in Toxæmias of Pregnancy". He says:

> Prognosis in preeclamptic toxæmia depends mainly on early diagnosis; this involves regular weighing . . . . Great emphasis is sometimes laid on a diet of low carbohydrate content and low caloric value to keep the weight down so that the patient does not gain more than three-quarters of a pound per week. I have never been convinced of the value of this, except in so far as the weight control is due to sodium restriction to prevent œdema.

It was I who laid great emphasis on the value of a high-protein, low-carbohydrate diet some years ago. In 1947 the average booked eclampsia rate at The Women's Hospital, Crown Street (taken over the previous eleven years), stood at one in 350 patients in spite of much conscientious antenatal care by the classical methods. In June, 1948, after discussing the problem with Dr. R. B. C. Stevenson, I asked the honorary medical staff at The Women's Hospital if I might give a daily lecture to all new patients on the value of a low-carbohydrate, high-protein diet.

Dr. Robert Macbeth, Miss J. Corden (the hospital's dietitian) and I gave these lectures every day for four years, and they reaped results far in excess of our hopes. Throughout these four years the booked eclampsia rate was lowered from one in 350 to approximately one in 7000 patients, and the incidence of severe preeclampsia fell remarkably. There was a marked fall in the number of surgical inductions required for preeclampsia and of course in the prematurity rate. There was a rich reward in the fœtal salvage (50 babies *per annum*).

As Professor Browne says, "The remarkable achievement in preventing eclampsia at The Women's Hospital, Crown Street, Sydney, has received world-wide recognition".

Many factors and many people contributed to this achievement in the years 1948 to 1952; but undoubtedly these lectures, which emphasized the value of a high-protein, low-carbohydrate diet, played an important part in the prophylaxis of toxæmia.

It is easily forgotten that all pre-cooked wheat and other grain products — *e.g.*, bread, biscuits, scones, cakes, pastries, buns and breakfast cereals — contain sodium bicarbonate or sodium chloride as an important added ingredient. My own investigations and those of McNaughton in 1948 showed that patients in Sydney who became toxæmic consumed much high-calorie refined carbohydrate carrying this complement of sodium.

One other word: Professor Browne states that the prognosis in preeclamptic toxæmia depends mainly on early diagnosis. But the diagnosis must be made much earlier than it classically is made. During the years 1948 to 1952, I searched for and treated toxæmia in its prehypertensive phase. We had to treble our ante-natal beds to allow this. Many patients are obviously toxæmic in appearance at the thirtieth week or earlier. The hypertensive phase may not become manifest until late in pregnancy or after labour begins. I have the complete records of 10 eclamptics who showed no rise of blood pressure (not even 5 millimetres) until a few days before the first fit occurred or until labour began.

If we take no action against toxæmia until we can measure it in numbers on a sphygmomanometer, we shall often be disappointed with our ante-natal care in this field.

Yours, etc.,

20 Victoria Avenue,
Rose Park,
South Australia.
August 20, 1957.

R. H. J. HAMLIN.

X-RAY THERAPY IN POST-TRAUMATIC ARTHRITIS, PARAARTHRITIS AND FASCIITIS.

SIR: I appreciate the letter from Dr. Gray, Dr. Collings, Dr. Beale and Dr. Main referring to my paper on this subject, as I believe the points they raise to be well considered. They come under two main headings: (*a*) the indication for, and place of, X-ray therapy, in the treatment of arthritis and paraarthritis; and (*b*) the possible dangers of such treatment.

I certainly did not intend to give the impression that X-ray therapy was the first line of attack indicated after a diagnosis of post-traumatic arthritis, paraarthritis or fasciitis is made. I entirely agree that immobilization, physiotherapy, hydrocortisone or local anæsthetic injections are very much simpler methods of treatment, and are efficacious in a majority of cases. It will be seen from the text and tables in my paper that over three-quarters of the cases were referred for X-ray therapy three months or longer after the development of the disability. The referring practitioners in the vast majority of cases were surgical or orthopædic specialists who frankly admitted that all routine methods of treatment had been tried without success. The cases sent for radiotherapy were, therefore, a selected group of chronic, non-responding, lesions in individuals whose bread-winning capacity had been impaired or lost over a prolonged period.

A request is made by your correspondents for further information as to the efficacy of X-ray therapy in chronic painful hip lesions in the aged, and also in paraarthritis of the shoulder. The treatment of degenerative osteoarthritis was purposely not considered in a paper strictly confined to post-traumatic arthritis. In any case, I would not venture to compare my experience in the former condition with that of authorities like Kahlmeter (1938), who described his results with radiotherapy in 5000 such cases. In general, one achieves marked relief of pain in less than half the cases of osteoarthritis of the hip, the night and resting pains being easier to relieve. As the degree of relief is independent of the degree of radiological destruction in the joint surfaces, I presume that the main action of irradiation is upon the capsule and periarticular structures. Relief of symptoms is maintained for six to 24 months in the majority.

With regard to paraarthritis of the shoulder, I did not elaborate the details, again because my series was small in comparison with others such as Steen and McCullough (1951), who described 300 such cases, and Kratzman and Frankel (1952), with 220 cases treated by radiotherapy. "Relief", in my series, means return to normal activity with freedom from pain (as distinct from stiffness, which takes longer to disappear). It is very kind of Dr. Gray, Dr. Collings, Dr. Beale and Dr. Main to describe relief within one week in 89% of these cases as being "truly remarkable"; but in actual fact, my results in this group are not as good as most. The authors referred to, among others, report relief in 95% to 98% within 24 to 48 hours when cases are treated in the acute or subacute phase, whereas the majority of my cases had passed into the chronic phase of "frozen shoulder".

Your correspondents mention the possible dangers of using X-ray therapy for non-malignant conditions, and suggest the possibility of skin cancer developing in the treated area. I would mention also the possibility of predisposing to leuchæmia, aplastic anæmia and osteogenic sarcoma, and also the danger of genetic changes if irradiation should reach the gonads. All these (except for the last, which is difficult to demonstrate) are complications which have been recorded as following X-ray therapy for benign conditions. They will be considered in sequence and their importance evaluated:

1. Cases of skin cancer, originating from five to 15 years after irradiation for benign dermatological or deep conditions, have been recorded. According to most reports, X-ray carcinoma results only after the production of one or two definite burns is followed by repeated exposure (as may occur in the treatment of chronic skin disease). In practically every case of post-irradiation carcinoma recorded, the skin had been previously damaged to the extent of inducing skin atrophy and telangiectasia, and no enlightened radiotherapist or dermatologist in these days would consider taking the skin to such a dose level in the treatment of benign conditions. However, in a predisposed skin, previously sensitized by environmental carcinogenic agents such as solar irradiation, coal tar, arsenicals, *etc.*, it is recognized that any non-specific traumatic agent (including a relatively small dose of X-ray therapy) may act as a "trigger mechanism" in the causation of skin cancer. This may account for the very occasional case of skin cancer reported to follow relatively low doses of X-ray therapy.

2. Court-Brown and Doll (1955) noted 28 deaths from leuchæmia and 12 from aplastic anæmia among 13,352 patients with ankylosing spondylitis treated by X-ray therapy in Britain. This incidence, although low, is 10 and 25 times, respectively, higher than would be expected in the normal population. It should be noted that in the majority of cases of ankylosing spondylitis, the whole of the spinal marrow is irradiated, and the dose given in many British centres is up to twice the dose level used in my series. Because of this danger, I have recently suggested, and shown the value of, localized irradiation in the upper lumbar region for ankylosing spondylitis (Stoll, 1957). Nevertheless, there can be no doubt that any irradiation of marrow-bearing bone must increase the risk of leuchæmia developing in an adult. The degree of risk obviously varies, but may be roughly compared to the danger, recently pointed out by Stewart *et alii* (1956), of leuchæmia developing in a child whose mother had a radiographic examination of her pelvis during pregnancy.

3. With regard to the possible development of bone sarcoma in X-ray irradiated tissue, Sabanos *et alii* (1956) analyzed 17 cases of their own, and 38 from the literature, to that date. They stress that its development requires a tissue dose of 3000*r* to 10,000*r*, although one case developed after 1400*r*. That it is a rare occurrence is shown by the fact that, of the hundreds of thousands of patients who have received heavy irradiation to the chest wall following radical mastectomy, the numbers of cases of rib sarcoma recorded in the literature can be numbered on the fingers of one hand. Recent years have introduced more potent causes of bone sarcoma. It has been calculated that the total irradiation received by the population of the world from radioactivity in the air following recent atomic explosions is only about 1% of the natural cosmic irradiation received by a person during his lifetime. Nevertheless, the Atomic Scientists' Association recently calculated that if one assumes no threshold dose for the induction of cancer, then the liberation of strontium 90 from recent hydrogen bomb blasts may already be responsible for some 50,000 cases of bone sarcoma developing in the future.

4. Natural cosmic irradiation, to which all mankind is exposed, has been calculated to contribute between 3*r* and 5*r* to the gonads during the course of a fertile lifetime. The generally accepted figure of the dose necessary to double the natural mutation rate is 50*r* per generation. It has

therefore been suggested that between 10r and 20r is the maximum safe exposure to the gonads during the fertile life of an individual in order to avoid increase in the mutation rate. Whereas the enlightened radiotherapist takes steps to avoid gonadal irritation during radiotherapy for benign conditions during fertile life, it should be noted that the average dose to the gonads from diagnostic radiology throughout life was calculated in the United States of America as equal and additional to the natural background dose.

One would be wise therefore to consider what results from irradiation therapy of non-malignant conditions would be as well accomplished by other modalities. Yet, in cases where radiotherapy can accomplish restoration to normal activity after simpler methods have failed, its use would appear to be justified as long as the risks to the patient are recognized, and therefore minimized, by the cognizant radiotherapist. This letter has pointed out the risks attached to radiodiagnostic procedures, and it is hoped that the enlightened radiodiagnostician, dermatologist and X-ray equipped physician will also take similar steps to minimize such dangers. As to the dangers from nuclear explosions, we must hope that the powers above will protect us.

Yours, etc.,

483 Little Lonsdale Street, Melbourne,
August 15, 1957.

BASIL A. STOLL.

References.

COURT-BROWN, W. M., and DOLL, R. (1957), "Leukæmia and Aplastic Anæmia in Patients Irradiated for Ankylosing Spondylitis", M. Res. Council of the Privy Council, Special Report Series No. 295.

KAHLMETER, G. (1938), *"Roentgenthérapie dans les maladies rhumatismales; expérience de plus de dix ans, fondée sur environ 5,000 cas et plus de 30,000 séances"*, *Acta radiol.*, 19: 529.

KRATZMAN, E. A., and FRANKEL, R. S. (1952), "Roentgen Therapy of Peritendinitis Calcarea of the Shoulder: A Study of 220 Cases with Late Results", *Radiology*, 59: 826.

SARANOS, A. O., *et alii* (1956), "Postradiation Sarcoma of Bone", *Cancer*, 9: 528.

STEEN, O. T., and MCCULLOUGH, J. A. L. (1951), "Supraspinatus Tendinitis—a Survey of 300 Consecutive Cases Treated by Roentgen Therapy", *Am. J. Roentgenol.*, 65: 245.

STEWART, A., *et alii* (1956), "Malignant Disease in Childhood and Diagnostic Irradiation in Utero", *Lancet*, 1: 447.

STOLL, B. A. (1957), "Ankylosing Spondylitis: Its Hormonal Background in Relation to X-ray Therapy", *J. Fac. Radiol.*, 8: 201.

SUTURES FOR CORNEAL GRAFTING.

SIR: In corneal grafting I find that much better results are obtained by using fine cotton rather than silk stitches. The silk seems to irritate the tissues and sets up an inflammatory reaction. I do not know the reason for this and am anxious to find out.

Yours, etc.,

105 St. George's Terrace, Perth,
August 10, 1957.

F. W. SIMPSON.

THE INFLUENZA EPIDEMIC.

SIR: Now that the recent influenza epidemic has eased off, may I ask the consultative committee in Victoria one or two questions? Was it considered unwise to ask the people to commence the usual home treatment of aspirin, sponges, fluids and rest when the symptoms of influenza were first noticed? The cryptic Press statement of "Asian 'flu is here" seemed to panic the public. Was it not possible to supply the general practitioner and his staff with the influenzal vaccine instead of inoculating the armed forces?

One final question, dealing with the future. As the general practitioner had thrust on him a sudden double, treble and occasionally quadruple amount of work through no choice of his own, his income will also suddenly rise. The person who will probably benefit most is the Deputy Commissioner of Taxation. Would the committee consider seeking a little relief in the taxation line?

I think the public as a whole have come through fairly well. A number of general practitioners handicapped by the disease themselves are still a little haggard. They would appreciate a "little break".

Yours, etc.,

Melbourne,
August 10, 1957.

"MELBOURNE G.P."

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Annual Subscription Course.

THE Post-Graduate Committee in Medicine in the University of Sydney announces the following lectures.

Professor A. Baird Hastings, Professor of Biological Chemistry in the University of Harvard, will speak on "Electrolytes of Tissues and Body Fluids", on Thursday, September 12, at 5 p.m., in the Stawell Hall, 145 Macquarie Street, Sydney; this lecture is suitable for clinicians. On Friday, September 13, at 4 p.m., in the Old Medical School, University of Sydney, Professor Hastings will lecture on "The Effects of Ions and Hormones on Carbohydrate Metabolism".

Professor R. Rimington, F.R.S., Professor of Chemical Pathology, University of London, a distinguished worker in hæmoglobin and porphyria, will give a lecture on "Biosynthesis of Hæm and Porphyrins" on Tuesday, October 1, at 4 p.m., in the Old Medical School, University of Sydney.

Week-End and Metropolitan Courses.

The week-end course in occupational medicine announced as taking place on November 30 and December 1 has been postponed, and will be held some time during the first half of 1958.

Fellowships.

The Senate of the University of Sydney has appointed Dr. J. S. Blow and Dr. J. W. Shand as Post-Graduate Training Fellows in Psychiatry for one year from August 1, 1957.

Film Appraisal Meeting.

The Post-Graduate Committee in Medicine in the University of Sydney announces that its next film appraisal meeting will be held on Wednesday, September 11, 1957, at 7.45 p.m., in the Post-graduate Theatrette, 131 Macquarie Street, Sydney, when the following films will be shown: "Stop Rheumatic Fever" (10 minutes); "Hæmorrhoids or Piles and the Early Detection of Rectal Cancer" (22 minutes); "Urinary Infection—Etiology, Diagnosis and Treatment" (18 minutes); "Treatment of Compound Fracture of the Long Bones Within Twelve Hours of Injury" (18 minutes). (This film was made at the Mater Hospital, Brisbane, by Dr. J. R. S. Lahz, the Honorary Orthopædic Surgeon.)

Medical practitioners interested in attending this meeting would be welcome, but in view of the limited accommodation they are asked first to communicate with the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephones: BU 4497-8.

LILLY FELLOWSHIP IN MEDICINE, 1957-1958.

DR. EWEN DOWNIE, Chairman of the Australian Lilly Fellowship Committee, has notified us that advice has been received from Dr. J. G. Evans, Secretary of the Lilly Foreign Educational Fellowship Committee, Eli Lilly and Company, Indianapolis, U.S.A., that Dr. John Barrymore Stokes of Western Australia has been awarded a Lilly Fellowship in Medicine for the year 1957-1958.

Research.

GRANTS FOR RESEARCH INTO CANCER.

ADVICE has been received from the Secretary of the New South Wales State Cancer Council to the effect that funds are available to the Council for further research into cancer. Applications are now being invited for grants in respect of (a) research Fellowships, (b) travelling Fellowships, (c) grants-in-aid.

The closing date for the lodgment of applications is October 21, 1957, and such applications must reach the Secretary, New South Wales State Cancer Council, Box 3944, G.P.O., Sydney, or 52 Bridge Street, Sydney, no later than that date. Application forms and further details may be obtained from the Secretary at the address mentioned above (Room 12, 6th Floor).

Congresses.

THIRD INTERNATIONAL CONGRESS OF ALLERGOLOGY.

THE third International Congress of Allergology will be held at the New Medical School, Paris, from October 19 to 26, 1958. The President of Honour is Pasteur Vallery-Radot (Paris), and the President is S. M. Feinberg (Chicago). A comprehensive scientific and social programme is being arranged. Information concerning the Congress may be obtained from the Secretary, Dr. B. N. Halpern, 197 Boulevard Saint-Germain, Paris, VII^{e}, France.

The College of General Practitioners.

VICTORIA FACULTY.

Pfizer Post-Graduate Week-End.

THE Victoria Faculty of the College of General Practitioners will conduct the Pfizer Post-Graduate Week-End at the Austin Hospital, Heidelberg, from October 4 to 6, 1957. On Saturday, October 5, the morning session will be as follows: "Abnormal Reactions to Drugs", Professor H. N. Robson (Professor of Medicine, University of Adelaide); "Management of Prolonged Labour", Dr. W. M. Lemmon; "Injuries to the Hand and Their Management", Mr. C. A. M. Renou. The afternoon session will consist of a discussion of cases in the wards by Professor Robson, a short discussion on "The Immediate Treatment of Spinal Injuries" by the staff of the Spinal Unit of the Austin Hospital, and a "brains trust" session conducted by the three lecturers.

As part of the Austin Hospital's seventy-fifth anniversary celebrations, the management is providing morning tea, lunch and afternoon tea for all participants. All members of the British Medical Association will be welcome.

University Intelligence.

THE UNIVERSITY OF MELBOURNE.

THE University of Melbourne Extension Committee announces the following lectures.

Lady Masson Memorial Lecture.

The fifth Lady Masson Memorial Lecture on Chemistry will be held on Wednesday, September 18, 1957, at 8.15 p.m., in the Masson Theatre, Chemistry School, University of Melbourne. The lecture will be delivered by Professor S. D. Rubbo, on the subject "Research in the Chemotherapy of Tuberculosis in Melbourne, Moscow and Elsewhere". All members of the medical profession are invited to be present. There is no charge for admission.

The Beattie-Smith Lectures.

The 23rd Beattie-Smith Lectures on insanity will be delivered by Dr. Norval Morris on Tuesday, September 24, and Tuesday, October 1, 1957, at 8.15 p.m., in the Anatomy Lecture Theatre, University of Melbourne. The subject of the first lecture will be "The Psychiatrist and the Criminal Law", and that of the second "The Psychiatrist and the Community". All members of the medical profession will be welcome at these lectures, which are free.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED AUGUST 17, 1957.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	2(1)	4(3)	..	..	2	..	..	..	8
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	1	..	6	..	..	..	..	..	7
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	..	9(8)	..	..	1(1)	..	..	1	11
Diphtheria	..	2(2)	..	..	..	..	..	..	2
Dysentery (Bacillary)	..	..	..	1(1)	..	..	..	..	1
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	21(9)	7(4)	..	7(6)	6(3)	4(2)	..	..	45
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	4	..	2	..	6
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	4(2)	5(5)	2	..	..	2	..	..	13
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	..	..	..	..	..	..	..
Puerperal Fever	..	..	..	1	..	..	1	..	2
Rubella	..	19(10)	..	38(8)	9(9)	..	..	..	66
Salmonella Infection	..	..	..	1	1(1)	..	..	..	2
Scarlet Fever	21(16)	11(10)	6	2(1)	4(4)	..	1	..	45
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	161	..	..	..	161
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	49(32)	5(4)	1	5(4)	11(5)	4(1)	2	..	77
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Public Health.

STAPHYLOCOCCAL PNEUMONIA.

We have been asked by the Director-General of Health, Commonwealth Department of Health, Canberra, to announce that he has sent the following telegram to the Commonwealth Directors of Health in all States of Australia:

> In view of the prevalence of staphylococcal pneumonia in some States you are authorized to permit erythromycin as a pharmaceutical benefit for this disease without previous use of penicillin or other drugs pending advice from the Pharmaceutical Advisory Committee.
>
> (Signed) METCALFE.

Medical practitioners who require erythromycin for the treatment of patients suffering from staphylococcal pneumonia should get into touch, either by telephone or otherwise, with the Commonwealth Director of Health in the particular State.

Australian Medical Board Proceedings.

QUEENSLAND.

THE following have been registered, pursuant to the provisions of Section 19 (1) (a) and (c) of *The Medical Acts*, 1939 to 1955, of Queensland: Williams, Reginald Hastings, M.B., B.S., 1955 (Univ. Queensland); Donnan, Alys Ester Patrica, M.B., B.Ch., B.A.O., 1955 (Univ. Belfast).

The following have been registered, pursuant to the provisions of Section 19 (1) (a) and (c) of *The Medical Acts*, 1939 to 1955, of Queensland: Skelton, Ester Isobel, M.B., B.S., 1955 (Univ. Melbourne); McKenzie, Nancy, M.B., B.S., 1950 (Univ. Sydney); Roper, John Ramsay, M.B., B.S., 1950 (Univ. Sydney); Bull, Graham MacGregor, F.R.C.P., 1952 (Univ. London).

The undermentioned person has been granted limited registration as a medical practitioner pursuant to Section 20 (3) of *The Medical Acts*, 1939 to 1955: Wall, Arnold William, M.B., B.S., 1957 (Univ. Sydney).

The following additional qualifications have been registered: Brophy, Teresa Rita O'Rourke, D.A., R.C.P., London; R.C.S., England, 1955; F.F.A., R.C.S., England, 1956.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Gonzwa, Jacob, M.D., 1921 (Univ. Cracow), 57 Darlinghurst Road, King's Cross, New South Wales.

Shearer, Charles Allan, M.B., B.S., 1951 (Univ. Sydney), 12 Butler's Road, Hurstville, New South Wales.

Endelman, Adolf Andrzej, L.L.M., R.C.P. and S. (Ireland), 1954, 33 Constitution Road, Dulwich Hill, New South Wales.

Murdock, Wallace Alexander, M.B., B.S., 1954 (Univ. Sydney), 61 Hull Road, West Pennant Hills, New South Wales.

Barat, Tibor Ernest, M.D., 1933 (Univ. Budapest), 11 Pacific Avenue, Bondi, New South Wales.

Medical Appointments.

Dr. D. B. Rosenthal has been appointed Director of Tuberculosis, Department of Health, Victoria.

Dr. B. R. Overend has been appointed a member of the Dental Board of New South Wales.

Dr. J. L. Frew has been appointed a member of the Victorian Nursing Council, Department of Health, Victoria.

Dr. J. H. W. Birrell has been appointed Police Surgeon, Chief Secretary's Department, Victoria.

Dr. L. T. Wedlick and Dr. B. T. Keon-Cohen have been appointed members of the Masseurs Registration Board, Department of Health, Victoria.

Dr. Wilma Scott has been appointed an officer of the State Psychological Clinic, Department of Health Services, Tasmania.

Dr. J. M. Collins has been appointed Resident Medical Officer for Mental Institutions, Hospitals Department, South Australia.

Deaths.

THE following deaths have been announced:

HARTNETT.—Leonard Hartnett, on August 17, 1957, at Malvern, Victoria.

MORRIS.—Emanuel Sydney Morris, on August 31, 1957, at Sydney.

Diary for the Month.

SEPT. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
SEPT. 12.—Queensland Branch, B.M.A.: Bancroft Oration.
SEPT. 13.—Queensland Branch, B.M.A.: Local Association Conference and Fork Dinner.
SEPT. 13.—Tasmanian Branch, B.M.A.: Branch Council.
SEPT. 14.—Queensland Branch, B.M.A.: Annual General Meeting.
SEPT. 16.—Victorian Branch, B.M.A.: Finance Subcommittee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, 88 L'Estrange Terrace, Kelvin Grove, Brisbane, W.1): All applicants for Queensland State Government Insurance Office positions are advised to communicate with the Honorary Secretary of the Branch before accepting posts.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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